Narrative Review Article

Understanding Endometriosis from an Interdisciplinary Lens: A Literature Review

Ananya Thota

The Athenian School, 2100 Mt Diablo Scenic Blvd, Danville, CA, 94506, United States

ABSTRACT

Endometriosis (EMS) is a chronic, estrogen-dependent, and progesterone-resistant inflammatory condition in which endometrial-like tissue is found outside the uterus, affecting 6-10% of reproductive-age women. Research has emerged on the genetic and biological associations of EMS, identifying biological pathways such as sex steroid hormone pathways and specific genes that may contribute to the disease phenotype. Despite this, there is uncertainty on how different findings across different scientific disciplines compare and inform the public on EMS pathogenesis. This paper synthesizes findings from the emerging genetic research and hormonal-associated studies and discusses how these findings contribute to our existing knowledge of EMS causes and progression. Understanding the intersectionality of biological mechanisms from different regulatory systems, relevant pathways, and how they contribute to the chronic and inflammatory nature of EMS, will deepen our knowledge of the disease pathology. Thus experts should also consider examining EMS from a more interdisciplinary perspective, such as conducting multi-system EMS studies and including diverse populations in EMS research as novel approaches for studying EMS and other reproductive-related diseases.

Keywords: Endometriosis; diagnostics; treatments; biomarkers; lesions; genetics; epigenetics; hormonal

INTRODUCTION

EMS is a chronic, systemic condition in which endometrial-like tissue grows outside the uterus, presenting as heterogenous lesions with multiple phenotypes, leading to pain, potential infertility, and a significantly reduced quality of life (1). The disease is estrogen-dependent and progesterone-resistant, affecting approximately 10% of reproductive age women, around the ages of 12 to 51 (1). This increases to up to 20-30% of women with subfertility, and 40-60% of women with pain and infertility (2). EMS is notoriously underdiagnosed due to disease heterogeneity and systemic barriers, where most women can have endometriosis for up to 7-10 years before diagnosis, often with symptoms present (3). Due to the elevated levels of estrogen in EMS patients compared to healthy patients, anti-estrogen therapies can serve to decrease abnormally high estrogen levels and manage symptoms. Anti-estrogen therapies decrease lesion growth and although they reduce symptoms, depending on age and severity, hormonal treatments such as anti-estrogen therapies are not

Corresponding author: Ananya Thota, E-mail: ananya.thota2008@gmail.com.

Accepted October 3, 2025
https://doi.org/10.70251/HYJR2348.35675683

always available as they can have a negative impact on menstruation, pregnancy, and bone health-- often causing bone density loss after 6 months (4). The cause of EMS remains unknown, and multiple theories have been suggested (5). The most widely accepted theory, proposed by Sampson in 1921, states that endometrial tissue fragments move retrograde through the fallopian tubes during menstruation, implanting into the pelvic cavity (6). Despite this, there is still a need to further characterize EMS pathology, especially as EMS remains overwhelmingly underdiagnosed. Understanding the prevalence and severity of EMS highlights the need for deeper investigation into the biological mechanisms and genetic basis of EMS, especially as they relate to current diagnostic and treatment struggles.

EMS is a highly heterogeneous condition, presenting in a range of anatomical subtypes and severities--ranging from patients being asymptomatic to debilitating pain. The substantial disease heterogeneity prevents the use of a universal set of biomarkers for EMS diagnosis, leading to a barrier in the diagnosis process. This has been shown through the failed validity of prior candidate biomarkers and diagnostic techniques, including the biomarker CA-125, originally identified from a study in 1998 and later in 2004, with 2,692 patients and 1,646 patients respectively (7-9). Nisenblat et al. performed a large systematic review of 141 studies assessing 122 blood biomarkers for EMS, and among the few biomarkers with sufficient data for meta-analysis, CA-125 was the most extensively studied, yet its diagnostic performance proved unreliable with reported sensitivities and specificities varying widely depending on the cut-off threshold (7). Higher sensitivity rankings are indicative of the biomarker being more effective at assessing whether women have EMS, whereas higher specificity rankings indicate the biomarker being more effective at correctly ruling out women who do not have EMS (7). The authors classified results as positive or negative against the reference standard of surgical visualization of EMS, and then applied a bivariate random-effects meta-analysis model to report summary values of specificity and sensitivity, which is a widely used and accepted statistical technique to assess the accuracy of clinical biomarkers as it accounts for study size and variability. At >10-14.7 U/mL dose, sensitivity, which is ranked out of 1, for CA-125 was 0.70 and specificity was 0.64, while at the more commonly used >35 U/ml dose, sensitivity dropped to 0.40 despite specificity rising to 0.91. This showed large variability for the CA-125 blood biomarker in its sensitivity and specificity, reflecting poor clinical utility (7). Additionally, abnormal menstrual symptoms can often be normalized, which also contributes to the delay in diagnosis (10). EMS phenotypes can manifest in three pelvic cavity subtypes: superficial peritoneal lesions, ovarian endometriomas, and deep infiltrating EMS (1). Some patients with extensive lesions can remain asymptomatic, while others with minimal disease can experience debilitating pain (11), suggesting that lesion burden and likely EMS phenotypes may not predict symptom severity. A better understanding of this heterogeneity through further research on EMS subtypes can help to progress subtype testing and tailored clinical approaches (12).

The 7–10-year delay of EMS diagnosis between symptom onset and diagnosis is partially due to the current diagnostic gold standard- laparoscopy- which is invasive, costly, and can be inaccessible due to resource limitations and socioeconomic barriers (13). While EMS has been primarily viewed as a hormone-driven disease, emerging research suggests it must be characterized as a multifaceted disorder involving immune dysregulation, genetic susceptibility, and inflammation (14). Genome-Wide-Association Studies (GWAS), familial aggregation studies, and twin studies have all provided compelling evidence that genetic susceptibility contributes towards EMS pathogenesis (15, 16). Specific genes such as Estrogen Receptor Alpha 1 (ESR1) and vezatin adherens junctions transmembrane protein (VEZT) associated with hormone regulation and inflammatory characteristics have been identified in previous studies (17). Thus, this paper aims to explore the biological mechanisms and pathways that contribute to EMS and synthesize genetic findings to better understand how these contribute to our current understanding of the chronic and inflammatory nature of the disease. This research review can ultimately provide insight into the need for studying EMS in more interdisciplinary contexts, such as examining whether a multi-system EMS study is required to obtain a more comprehensive perspective on biological mechanisms underlying EMS and possibly other reproductive diseases.

EMERGING GENETICS RESEARCH IN EMS

There is increasingly prevalent evidence suggesting that genetic susceptibility may contribute towards an increased risk of EMS. Monozygotic twin studies estimate that genetic factors account for ~50% of

the variance in EMS susceptibility (18, 19). Familial aggregation studies have also supported this idea through showing that first-degree relatives of diagnosed EMS patients have an elevated risk of developing EMS, suggesting a genetic predisposition (14). GWAS studies, used to identify genomic variations and finding genetic markers, have identified multiple risk loci associated with EMS in a diverse group of multi-ethnic individuals from countries including the United Kingdom and Japan, implicating genes involved in sex steroid hormone pathways (15, 17). This gene mapping technique uses SNPs to evaluate the genome for risk-associated variations (15). Recent studies have also explored the role of epigenetic changes and non-coding RNAs in EMS disease development (20-22). Altered expressions of long non-coding RNAs (IncRNAs) have been linked to progesterone resistance and inflammation regarding EMS pathophysiology (23). These findings give strong insight into how gene regulatory mechanisms may contribute to hormonal and inflammatory characteristics of EMS.

Familial studies have provided further evidence of heritability in EMS (18, 19, 24). For example, Treloar et al. surveyed 3,298 female monozygotic and dizygotic twins and found that 215 of 3,096 respondents reported endometriosis (≈7%) (18). Concordance was significantly higher in monozygotic twins ($r = 0.46–0.52$) than in dizygotic twins ($r = 0.19–0.28$), indicating that roughly half of the variance in liability can be attributed to genetic factors (18). These findings provide evidence of EMS heritability. Additionally, during 1977-1982, Dalsgaard et al. conducted a controlled historical cohort study of women from an age group of 15-49 years old in Denmark with a 33-year-follow up (24). There were 24,591 women diagnosed with EMS who were compared with 98,764 women without EMS (24). With a nearly 100% follow-up rate, disregarding the 4-6% of women who emigrated, daughters of the women with EMS had a 2.12-fold (95% confidence interval 1.89-2.37, $P<0.0001$) increased rate of diagnosis with EMS in comparison to the daughters of the women without EMS, strengthening evidence for a heritable predisposition to EMS (24). EMS that occurs in families tends to be more phenotypically and symptomatically severe than sporadic cases of EMS, showing that those with these severe manifestations of EMS are more likely to have affected offspring or siblings, indicating that EMS risk increases if there is a history of EMS in relatives (20). Thus, there is stronger genetic predisposition in individuals with severe EMS phenotypes. While studies have demonstrated strong familial clustering, indicating heritability, studies performed on animal models including rhesus monkeys show that the disease does not follow simple Mendelian genetic patterns (25). Thus, investigating modes of genetic inheritance in EMS animal models may offer insight into mechanisms underlying increased risk in families with EMS-diagnosed relatives.

GWAS has offered promising data for understanding potential causes of EMS (26). Studies, such as the large genome-wide association meta-analysis by Rahmioglu et al, performed on multi-ethnic groups of individuals have been key in identifying the specific loci associated with the disease, pinpointing over a dozen risk loci across diverse populations: ESR1 (estrogen receptor alpha), CYP19A1 (aromatase), and HSD17B1, all central to estrogen synthesis and responsiveness, aligning with the existing knowledge that EMS is an estrogen-dependent disease. Other significant loci identified are WNT4, which plays a role in the reproductive tract development; VEZT, which is involved in cell implantation and adhesion; and GREB1, which is also estrogen-responsive (15, 27). Potential utilities of these findings from these studies include an improved understanding of EMS pathogenesis, discovery and exploration of disease subtypes, and risk prediction.

Epigenetics has been shown to play a role in EMS disease phenotypes (28). Basic mechanisms of epigenetics include DNA methylation, which often silences or reduces gene expression; histone modification, affecting how tightly DNA is wound and affecting accessibility of DNA for transcription of genes in that specific region; and noncoding RNA (ncRNA), which prevents the messenger RNA (mRNA) from being translated into proteins. Epigenetic processes have been shown to contribute to other human diseases such as breast cancer, Huntington's, Alzheimer's, and Parkinson's diseases, by changing gene expression and regulating cellular processes including apoptosis and immune responses (21, 29). The development of EMS complications such as pain and infertility have been linked to abnormal epigenetic modifications (28). Epigenetic dysfunction, which are abnormal changes in the epigenetic regulation of gene expression, seem to play a pivotal role in the pathogenesis of EMS (28). Women with EMS have abnormal levels of enzymes called DNA methyltransferases (DNMTs), especially in endometrial tissues, which control gene activity through DNA methylation (30). Additionally, the eutopic endometrium, the normal lining of the uterus,

are reported to be hypoacetylated in women with EMS, which occurs when a histone has fewer acetyl groups, compared to eutopic endometrium without EMS presentation. This reduces gene expression of inflammatory and steroid hormone signaling pathways, which can affect important cellular processes like inflammation and hormone response (31). ncRNAs regulate gene expression post-transcription, and in EMS, their abnormal regulation disrupts pathways involved in inflammation and hormone signaling. Furthermore, microRNAs (miRNAs), which play important regulatory roles for cleavage or degradation of mRNA, have been shown to be altered in both ectopic endometrium, endometrial tissue found elsewhere in the body, and eutopic endometrium tissues in women with EMS (32). These findings overall highlight how disruptions in epigenetic regulation of EMS-related pathways contribute significantly to EMS, pointing towards epigenetics as a promising area of research in understanding this disease.

BIOLOGICAL PATHWAYS IDENTIFIED IN EMS

Endometriosis' pathophysiology is multifaceted and complex. Its estrogen dependence and progesterone resistance play key roles in the abnormal growth of endometrial-like tissue outside the uterus (1, 33). Estrogen promotes angiogenesis, the process where new blood vessels form from existing ones; cellular proliferation, the process regarding cell growth and division; and the expression of inflammatory cytokines such as IL-1β and TNF-α, signaling molecules that amplify inflammation (23, 34). Progesterone functions in suppressing these processes, and in EMS patients, progesterone receptor expression is often dysregulated or reduced, which Reis et al. determined through a comprehensive screening of previously published research dating to 1958 (23, 34). In addition, peritoneal fluid samples collected during laparoscopy from EMS patients have shown that patients tend to present with elevated levels of pro-inflammatory cytokines, oxidative stress in the peritoneal environment, and macrophage activation, contributing to immune evasion and allowing ectopic lesions to thrive (35). This was demonstrated by comparing the expression of estrogen receptors and inflammatory cytokines in macrophages obtained from peritoneal fluid samples from 30 women with EMS to the samples of 22 women without EMS, serving as experimental controls (35). Angiogenic factors such as vascular endothelial growth factor (VEGF) are upregulated, promoting the formation of new blood vessels to support lesion survival (36).

Disruptions in the endocrine system have been shown to play a central role in the progression and presentation of EMS. The hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress and hormonal balance, may be disrupted in EMS patients, linking EMS to broader systemic and neuroendocrine dysfunctions (37). Regarding endocrine changes in EMS, researchers utilized GWAS to pinpoint single nucleotide polymorphisms (SNPs) in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and changes in estrogen and estrogen receptors; progesterone and progesterone receptors; inhibin, activin and follistatin; and anti-mullerian hormone in EMS patients (37). These hormones are known to regulate ovarian function and reproductive hormone signaling, among other functions. Further characterizing biomarkers from different regulatory systems associated with EMS can help us to further reveal the complexity of EMS causes and progression, pointing towards possible candidate biomarkers.

EMS lesions are central to its pathology, and they exhibit increased nerve fiber density and fibrosis which contributes to chronic pelvic pain. Previous studies have shown that EMS supports neuroangiogenesis, the process in which new nerve fibers and blood vessels form. For example, the expression of nerve growth factor (NGF), which plays a crucial role in the survival and development of nerve cells and is increased in EMS lesions (38). In this study they used immunohistochemistry and measured NGF protein expression, and found that NGF levels were significantly higher in EMS lesions compared to non-lesion endometrium. This can also increase the presence of nociceptors, specialized nerve cell endings that initiate the body's sensation of pain, as well as increasing the density of nerve fibers (38). The pathological growth of nerve fibers in EMS lesions is associated with chronic pelvic pain in EMS patients. Due to the lack of an intrinsic nerve supply in ectopic EMS lesions in the peritoneal cavity, new nerve fibers are formed to transmit pain signals due to EMS lesions, leading to an increased density of nerve fibers as shown through immunohistochemical staining for GAP-43–positive sensory nerve fibers (39). Additionally, the expression of growth-associated protein 43, a protein crucial to neuronal growth and regeneration, is elevated in nerves closer to EMS lesions than in nerves that are distant

from those lesions (40). Thus, neuroangiogenesis within EMS lesions likely plays a central role in the pelvic pain experienced by EMS patients.

Previously published research has also shown that one of the hallmarks of EMS progression is immune system dysfunction. Immune cells such as neutrophils and peritoneal macrophages aid in processes such as endometriotic cell growth and angiogenesis (41). Peritoneal macrophages and natural killer (NK) cells in EMS patients cannot eliminate endometrial cells as effectively in the peritoneal cavity compared to healthy patients due to abnormal receptor-ligand interactions, elevated levels of immunosuppressive cytokines, and dysfunction of adhesion molecules (42). Additionally, the imbalance between the Th1/Th2 immune cells induces lesion progression as it leads to abnormal cytokine secretion as well as inflammation (41). The presence of anti-EMS antibodies in both the peritoneal fluid and patient serum has been found in patients diagnosed with EMS (43). Confino et al. demonstrated this through investigating autoantibodies in 14 laparoscopically diagnosed EMS and 9 control patients, undergoing laparoscopic tubal occlusion, in both peritoneal fluid and serum. Results from this study showed an abnormal concentration of anti-phospholipids and anti-histones antibodies within the peritoneal cavity of EMS patients relative to control patients, demonstrating that these elevated antibodies may serve as a proxy for EMS pathology (43). The autoantibodies could potentially stimulate the immune system and perpetuate inflammation in women with EMS. Furthermore, there appears to be an increase in EMS occurrence correlating with immune-related diseases, indicating a pathophysiologic pathway shared between EMS and the immune system (44). As studies increasingly highlight a connection between EMS and the immune system, it is essential to establish the type of primary and secondary immune response cells such as macrophages and memory B cells in future EMS research, as well as their relationship to different phenotypes, symptoms, and stages of the disease.

CONCLUSION

While recent genetic and molecular breakthroughs in EMS have been transformative, there are several limitations present in the current body of research. One major challenge in research lies in the population being investigated in EMS studies. While slightly more European and Asian women are diagnosed compared to Hispanic and black women, this doesn't necessarily correlate to a higher prevalence among European and Asian women and may highlight a barrier to diagnosis for groups not included in these studies (45). Though recent studies have tried to diversify which ethnic populations are included in EMS research, many of the major studies have been performed in European populations (27). As a result, many of the identified risk loci, while insightful, aren't broadly applicable to diverse populations of women who are at risk for developing EMS. Additionally, despite promising results in recent EMS research, including an increase in EMS-associated genetic markers identified, very few biomarkers have been successfully translated into clinical tools. Most of these findings lack clinical validation, and their predictive power is insufficient for individual risk assessment or treatment plans. This highlights a significant bench-research-to-clinic gap and limits their immediate applicability.

A research area that warrants increased attention is understanding subtype-specific and EMS disease heterogeneity. As demonstrated in Table 1, the current diagnostic and treatment strategies often ignore the wide range of lesion subtypes, symptom variability, and hormonal responsiveness. This causes severe delays in diagnosis, making it significantly harder for many women to begin treatment, in turn, likely causing issues from EMS-related symptoms longer. The lack of tailored treatment to patients with heterogenous symptoms often leads to inefficient treatment, making it crucial that this aspect of diagnostic research is highlighted.

Despite these limitations, several promising directions could enhance the utility of genetic findings in clinical care. The development of polygenic risk scores tailored to diverse populations could help researchers understand the basis of disease heterogeneity across EMS patients, and result in an increased understanding of genetic susceptibility amongst specific populations and potentially inform early intervention (46). While blood-based markers and other biomarkers aren't accurate yet due to a lack of knowledge regarding the heterogeneity of EMS, further characterization of regulatory systems and their associated molecular biomarkers in diverse populations such as specific non-Eurocentric groups can enhance clinical applicability of genetics findings associated with EMS in the future. For example, a deeper characterization of genetic and hormonal underpinnings of EMS amongst different populations can help with understanding the

Table 1. Standard of Care Treatments Advantages and Disadvantages

Treatment	Description	Advantages	Disadvantages
Hormonal Treatment	Focuses on estrogen suppression- includes oral contraceptive pills	Generally accessible, treats dysmenorrhea and chronic pelvic pain	Not effective in all patients
Gonadotropin-releasing hormone agonists	Second-line treatment that suppress estrogen substantially such as Elagolix	More effective for chronic pain and other EMS symptoms	Significant risk of bone loss, heat flashes- prevents general long term use
Non Steroidal Anti Inflammatory Drugs (NSAIDs)	Used for pain management- includes Advil and combinations like Analgesia	Very accessible, mildly effective on pain depending on pain levels	Not useful in treating EMS symptoms aside from pain, and not fully effective
Opioids	Used for more severe pain management	Very effective for short-lived pain	Highly addictive, not recommended for long term use
Laparoscopy	Surgical removal of lesions	Diagnostic and can help manage symptoms such as pain	Invasive, costly, and inaccessible

complexity of EMS disease progression and how it may differentially develop within and between different ethnic populations. Thus, it is important for the field to consider investigating whether differences in genomic variants such as SNPs amongst different human ethnic populations with EMS-related symptoms correlate with EMS disease heterogeneity and whether specific variants between populations may be responsible for distinct EMS-associated symptoms. Such research may provide insight into the identification of specific biomarkers associated with Eurocentric and/or non-Eurocentric populations and may enhance our understanding of how molecular components from different regulatory systems interact with one another to reinforce EMS-associated symptoms and other reproductive-related diseases in women.

Endometriosis is a multi-faceted condition with significant genetic and biological complexity. Recent studies have identified risk loci and key genes, particularly those involved in sex steroid hormone pathways, inflammation, and cell adhesion, contributing to the disease's pathophysiology. Advances in GWAS and epigenetic research studies have revealed that similar to other human diseases, EMS is a heritable disease and that challenges in understanding its heterogeneous symptoms persist. Moving towards a greater and broader understanding of EMS disease heterogeneity and its associated candidate biomarkers is of utmost importance. This is pivotal in order to move identified biomarkers towards clinical validation and subsequent testing. Overall, such findings may point towards the development of non-invasive diagnostic approaches, especially as emerging research provides insight into EMS-associated regulatory systems and novel candidate biomarkers, which may lay the groundwork towards improving standard of care for EMS-diagnosed patients.

ACKNOWLEDGEMENTS

I acknowledge and thank my mentor, Brianna A. Parrington, a PhD candidate from the University of California, Berkeley, for helping me conduct this research and providing guidance in writing this review paper, and the Lumiere Program for providing support for writing and publishing this review.

FUNDING SOURCES

This work was supported by Lumiere LLC.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Zondervan KT, Becker CM, and Missmer SA. Endometriosis. *N. Engl. J. Med*. 2020; 382: 1244–

1256. https://doi.org/10.1056/NEJMra1810764
2. Bulun SE. Endometr. *New Engl. J. Med*. 2009; 360: 268–279. https://doi.org/10.1056/NEJMra0804690
3. Swift B, Taneri B, Becker CM, et al. Prevalence, Diagnostic Delay and Economic Burden of Endometriosis and Its Impact on Quality of Life: Results From an Eastern Mediterranean Population. *European Journal of Public Health*. 2024; 34 (2): 244–252. https://doi.org/10.1093/eurpub/ckad216
4. Cho YH, Um MJ, Kim SJ, Kim SA & Jung H. Raloxifene Administration in Women Treated with Long Term Gonadotropin-releasing Hormone Agonist for Severe Endometriosis: Effects on Bone Mineral Density. *Journal of menopausal medicine*. 2016; 22 (3): 174–179. https://doi.org/10.6118/jmm.2016.22.3.174
5. Sourial S, Tempest N & Hapangama DK. Theories on the pathogenesis of endometriosis. *International journal of reproductive medicine*. 2014; 2014: 179515. https://doi.org/10.1155/2014/179515
6. Sampson J. Peritoneal endometritis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am. J. Obstet. Gynecol*. 1927; 14: 442–469. https://doi.org/10.1016/S0002-9378(15)30003-X
7. Nisenblat V, Bossuyt PM, Shaikh R, Farquhar C, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. *The Cochrane database of systematic reviews*. 2016; 2016 (5): CD012179. https://doi.org/10.1002/14651858.CD012179
8. Molo MW, Kelly M, Radwanska E & Binor Z. Preoperative serum CA-125 and CA-72 in predicting endometriosis in infertility patients. *The Journal of reproductive medicine*. 1994; 39 (12): 964–966.
9. Somigliana E, Viganò P, Tirelli AS, Felicetta I, et al. Use of the concomitant serum dosage of CA 125, CA 19-9 and interleukin-6 to detect the presence of endometriosis. Results from a series of reproductive age women undergoing laparoscopic surgery for benign gynaecological conditions, Human Reproduction. August 2004; 19 (8): 1871–1876. https://doi.org/10.1093/humrep/deh312
10. Hudelist G, Fritzer N, Thomas A, Niehues C, et al. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Human reproduction (Oxford, England)*. 2012; 27 (12): 3412–3416. https://doi.org/10.1093/humrep/des316
11. Vercellini P, Fedele L, Aimi G, Pietropaolo G, et al. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: A multivariate analysis of over 1000 patients. *Hum. Reprod*. 2007; 22: 266–271. doi: 10.1093/humrep/del339
12. Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertility and sterility*. 2014; 102 (5): 1223–1232. https://doi.org/10.1016/j.fertnstert.2014.07.1244
13. Hsu AL, Khachikyan I & Stratton P. Invasive and noninvasive methods for the diagnosis of endometriosis. *Clinical obstetrics and gynecology*. 2010; 53 (2): 413–419. https://doi.org/10.1097/GRF.0b013e3181db7ce8
14. Taylor HS, Kotlyar AM & Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet (London, England)*. 2021; 397 (10276): 839–852. https://doi.org/10.1016/S0140-6736(21)00389-5
15. Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. *Hum Reprod Update*. 2014 Sep-Oct; 20 (5): 702-16. doi: 10.1093/humupd/dmu015. Epub 2014 Mar 27. PMID: 24676469; PMCID: PMC 4132588.
16. Chiorean DM, Mitranovici M-I, Toru HS, Cotoi TC, et al. New Insights into Genetics of Endometriosis — A Comprehensive Literature Review. *Diagnostics*. 2023; 13 (13): 2265. https://doi.org/10.3390/diagnostics13132265
17. Sapkota Y, Steinthorsdottir V, Morris P, Fassbender A, et al. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. *Nat. Commun*. 2017; 8: 15539.
18. Treloar SA, O'Connor DT, O'Connor VM & Martin NG. Genetic influences on endometriosis in an Australian twin sample. sueT@qimr.edu.au. *Fertility and sterility*. 1999; 71 (4): 701–710. https://doi.org/10.1016/s0015-0282(98)00540-8
19. Nyholt DR, Gillespie NG, Merikangas KR, Treloar SA, Martin NG & Montgomery GW. Common genetic influences underlie comorbidity of migraine and endometriosis. *Genetic epidemiology*. 2009; 33 (2): 105–113. https://doi.org/10.1002/gepi.20361
20. Kennedy S, Hadfield R, Mardon H & Barlow D. Age of onset of pain symptoms in non-twin sisters concordant for endometriosis. *Human reproduction (Oxford, England)*. 1996; 11 (2): 403–405. https://doi.org/10.1093/humrep/11.2.403
21. Naeini MM & Ardekani AM. Noncoding RNAs and Cancer. *Avicenna journal of medical biotechnology*. 2009; 1 (2): 55–70.
22. Zubrzycka A, Zubrzycki M, Perdas E & Zubrzycka M. Genetic, Epigenetic, and Steroidogenic

Modulation Mechanisms in Endometriosis. *Journal of clinical medicine*. 2020; 9 (5): 1309. https://doi.org/10.3390/jcm9051309

23. Reis FM, Coutinho LM, Vannuccini S, Batteux F, Chapron C, Petraglia F. Progesterone receptor ligands for the treatment of endometriosis: the mechanisms behind therapeutic success and failure. *Hum Reprod Update*. 2020 Jun 18; 26 (4): 565-585. doi: 10.1093/humupd/dmaa009. PMID: 32412587; PMCID: PMC7317284.
24. Dalsgaard T, Hjordt Hansen MV, Hartwell D, Lidegaard O. Reproductive prognosis in daughters of women with and without endometriosis. *Hum Reprod*. 2013 Aug; 28 (8): 2284-8. doi: 10.1093/humrep/det231. Epub 2013 May 21. PMID: 23696543.
25. Zondervan KT, Weeks DE, Colman R, Cardon LR, et al. Familial aggregation of endometriosis in a large pedigree of rhesus macaques. *Human reproduction (Oxford, England).* 2004; 19 (2): 448–455. https://doi.org/10.1093/humrep/deh052 24.
26. Marees AT, de Kluiver H, Stringer S, Vorspan F, et al. A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. *International journal of methods in psychiatric research*. 2018; 27 (2): e1608. https://doi.org/10.1002/mpr.1608
27. Albertsen HM, Chettier R, Farrington P, Ward K. Genome-wide association study link novel loci to endometriosis. *PLoS One.* 2013; 8 (3): e58257. doi: 10.1371/journal.pone.0058257. Epub 2013 Mar 5. PMID: 23472165; PMCID: PMC3589333.
28. Hsiao KY, Wu MH & Tsai SJ. Epigenetic regulation of the pathological process in endometriosis. *Reproductive medicine and biology.* 2017; 16 (4): 314–319. https://doi.org/10.1002/rmb2.12047
29. Moosavi A & Motevalizadeh Ardekani A. Role of Epigenetics in Biology and Human Diseases. *Iranian biomedical journal.* 2016; 20 (5): 246–258. https://doi.org/10.22045/ibj.2016.01
30. Wang L, Zhao J, Li Y, Wang Z & Kang S. Genome-wide analysis of DNA methylation in endometriosis using Illumina Human Methylation 450 K BeadChips. *Molecular reproduction and development.* 2019; 86 (5): 491–501. https://doi.org/10.1002/mrd.23127
31. Monteiro JB, Colón-Díaz M, García M, Gutierrez S, et al. Endometriosis is characterized by a distinct pattern of histone 3 and histone 4 lysine modifications. Reproductive sciences (Thousand Oaks, Calif.), 2014; 21 (3): 305–318. https://doi.org/10.1177/1933719113497267
32. Hull ML & Nisenblat V. Tissue and circulating microRNA influence reproductive function in endometrial disease. *Reproductive biomedicine online*. 2013; 27 (5): 515–529. https://doi.org/10.1016/j.rbmo.2013.07.012
33. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, et al. Endometriosis. *Endocrine reviews*. 2019; 40 (4): 1048–1079. https://doi.org/10.1210/er.2018-00242
34. Podgaec S, Abrao MS, Dias JA, Jr, Rizzo LV, et al. Endometriosis: an inflammatory disease with a Th2 immune response component. *Human reproduction (Oxford, England).* 2007; 22 (5): 1373–1379. https://doi.org/10.1093/humrep/del516
35. Montagna P, Capellino S, Villaggio B, Remorgida V, et al. Peritoneal fluid macrophages in endometriosis: correlation between the expression of estrogen receptors and inflammation. *Fertility and sterility.* 2008; 90 (1): 156–164. https://doi.org/10.1016/j.fertnstert.2006.11.200
36. Young SL. Nonsurgical approaches to the diagnosis and evaluation of endometriosis. *Fertility and sterility.* 2024; 121 (2): 140–144. https://doi.org/10.1016/j.fertnstert.2023.12.020
37. Méar L, Herr M, Fauconnier A, Pineau C, Vialard F. Polymorphisms and endometriosis: a systematic review and meta-analyses. *Hum Reprod Update.* 2020 Jan 1; 26 (1): 73-102. doi: 10.1093/humupd/dmz034. PMID: 31821471.
38. Pezet S & McMahon SB. Neurotrophins: mediators and modulators of pain. *Annual review of neuroscience.* 2006; 29: 507–538. https://doi.org/10.1146/annurev.neuro.29.051605.112929
39. Asante A & Taylor RN. Endometriosis: the role of neuroangiogenesis. *Annual review of physiology.* 2011; 73: 163–182. https://doi.org/10.1146/annurev-physiol-012110-142158
40. Mechsner S, Schwarz J, Thode J, Loddenkemper C, et al. Growth-associated protein 43-positive sensory nerve fibers accompanied by immature vessels are located in or near peritoneal endometriotic lesions. *Fertility and sterility.* 2007; 88 (3): 581–587. https://doi.org/10.1016/j.fertnstert.2006.12.087
41. Podgaec S, Abrao MS, Dias JA, Jr, Rizzo LV, et al. Endometriosis: an inflammatory disease with a Th2 immune response component. *Human reproduction (Oxford, England).* 2007; 22 (5): 1373–1379. https://doi.org/10.1093/humrep/del516
42. Jiang W, Xu W & Chen F. Dysfunction of natural killer cells promotes immune escape and disease progression in endometriosis. *Frontiers in immunology*. 2025; 16: 1657605. https://doi.org/10.3389/fimmu.2025.1657605
43. Confino E, Harlow L, Gleicher N. Peritoneal fluid and serum autoantibody levels in patients with endometriosis. *Fertil Steril*. 1990 Feb; 53 (2): 242-5. doi: 10.1016/s0015-0282(16)53274-9. PMID: 2298309.

44. Shigesi N, Kvaskoff M, Kirtley S, Feng Q, et al. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. *Human reproduction update.* 2019; 25 (4): 486–503. https://doi.org/10.1093/humupd/dmz014
45. Farland LV & Horne AW. Disparity in endometriosis diagnoses between racial/ethnic groups. BJOG : an international journal of obstetrics and gynaecology, 2019; 126 (9): 1115–1116. https://doi.org/10.1111/1471-0528.15805
46. Vannuccini S, Clemenza S, Rossi M & Petraglia F. Hormonal treatments for endometriosis: The endocrine background. *Reviews in endocrine & metabolic disorders.* 2022; 23 (3): 333–355. https://doi.org/10.1007/s11154-021-09666-w