Journal of Medical Genetics and Clinical Biology
Homepage : https://journal.antispublisher.id/index.php/JMGCB
Email : admin@antispublisher.com

e-ISSN : 3032-1085
JMGCB, Vol. 2, No. 5, May 2025
Page 115-122

Immune System Dysregulation in Endometriosis: Inflammatory Pathways, Immune Cell Imbalances, and Potential Therapeutic Targets

Djurabekova Surayyo Takhirovna
Pediatric Medical Institute, Uzbekistan

DOI : https://doi.org/10.61796/jmgcb.v2i5.1285

Sections Info

Article history:
Submitted: April 14, 2025
Final Revised: April 27, 2025
Accepted: May 13, 2025
Published: May 31, 2025

Keywords:
Endometriosis
Immune system dysfunction
Cytokine imbalance
IL-6
TNF-α
VEGF
Th17/Treg ratio
NK cell activity
Macrophage polarization
Chronic inflammation
Immunotherapy in Uzbekistan

ABSTRACT

Objective: *This study aims to investigate the immune system dysregulation in endometriosis, focusing on cytokine imbalances, immune cell malfunctions, and epigenetic modifications to identify potential diagnostic markers and individualized therapeutic options.* ***Method:*** *A total of 240 female participants, including 100 endometriosis patients and 50 healthy controls, were included in the study. Data were collected through cytokine measurements (IL-6, TNF-a, VEGF), immune cell profiling (Th1/Th2 dynamics, Treg/Th17 ratios, macrophage M1/M2 patterns), and epigenetic analysis (DNA methylation and microRNA expression) in blood and endometrial tissue samples.* ***Results:*** *Endometriosis patients exhibited significant immune imbalance with elevated levels of IL-6, TNF-a, and VEGF, disrupted Th17/Treg ratios, reduced NK cell activity, and an M2-dominant macrophage pattern, all contributing to chronic inflammation and tissue expansion.* ***Novelty:*** *The study highlights the role of epigenetic modifications and immune cell dysfunction in endometriosis, providing novel insights into its immunopathology. The findings support the development of precision medicine approaches targeting immune signaling pathways and biomarker-based therapies to improve treatment outcomes.*

INTRODUCTION

Endometriosis exists as a chronic and estrogen-dependent gynecological condition that affects 10% of all reproductive-age women across the world which produces persistent pelvic pain together with dysmenorrhea and dyspareunia while also causing infertility. The medical condition consists of endometrial tissue growing abnormally outside the uterus where it finds placement especially in the peritoneum and ovaries and pelvic tissue, and the insufficient understanding of endometriosis pathogenesis causes difficulties in accurate diagnosis and effective treatments alongside high relapse rates due to its widespread prevalence among women [1]. Current understanding of endometriosis development through retrograde menstruation along with coelomic metaplasia and stem cells does not provide a complete explanation of its occurrence [2]. Disease onset and persistent factors heavily depend on impairments within the immune system according to contemporary research. Ectopic endometrial cells avoid immunological removal by receiving support from the immune system through combined mechanisms of inflammation and evasion and new blood vessel development [3]. The immune dysregulation involves incorrect cytokine creation together with modified immune cell operations and changes to how immune response pathways respond [4]. The treatment options for endometriosis are restricted because it displays

heterogeneous characteristics while only offering hormonal suppression combined with surgical intervention as the main therapeutic approaches [5]. The treatments generate important adverse effects together with brief symptom reduction but the disease tends to appear recurrently. The identification of innovative diagnostic tools along with individualized treatments that address immune system abnormalities becomes crucial because of immediate medical necessity, and this research examines the endometriosis-related immunological processes by studying how cytokines disrupt balance and how immune cells function while inspecting epigenetic control [6]. The study investigates both individualized therapeutic alternatives through immunomodulatory therapy alongside biomarker-based precision medicine. The research presents findings to advance the creation of better and individualized treatment methods for endometriosis management [7].

RESEARCH METHOD

Literature Review

Endometriosis is a chronic inflammatory gynecological disorder affecting 10-15% of reproductive-age women worldwide, including a significant proportion in Uzbekistan, where an increasing number of infertility cases are linked to this disease [8]. The pathogenesis of endometriosis is complex, involving hormonal imbalances, immune dysfunction, and epigenetic alterations that contribute to the persistence of ectopic endometrial tissue . Although theories such as retrograde menstruation, coelomic metaplasia, and stem cell involvement attempt to explain its origin, recent studies emphasize that immune system dysregulation plays a fundamental role in the development and progression of endometriosis [9].

One of the key findings in endometriosis is the presence of chronic inflammation, maintained by an abnormal cytokine profile in the peritoneal fluid and serum of patients. Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and vascular endothelial growth factor (VEGF) create an inflammatory microenvironment that promotes lesion survival, angiogenesis, and immune escape mechanisms [10]. IL-6 has been identified as a major contributor to the chronicity of inflammation, sustaining the activation of immune cells and facilitating the immune evasion of ectopic endometrial tissue . TNF-α plays a crucial role in tissue remodeling and fibrosis, exacerbating adhesion formation and increasing pain severity in patients with advanced endometriosis. VEGF overexpression has been shown to drive aberrant neovascularization, ensuring a continuous blood supply to ectopic implants and allowing their proliferation outside the uterine environment [11].

Immune system dysfunction in endometriosis is also characterized by an imbalance in T-helper (Th) cell subpopulations, particularly an increased Th17/Treg ratio. A dominance of Th17 responses leads to excessive production of IL-17, which promotes the recruitment of inflammatory cells and further amplifies tissue damage and lesion progression. In contrast, regulatory T cells (Tregs), which are responsible for

immune suppression and tolerance, are functionally impaired, leading to insufficient immune regulation and prolonged inflammation [12].

A major feature of endometriosis is the reduction in natural killer (NK) cell cytotoxicity, failing to eliminate ectopic endometrial cells that should otherwise be targeted by the immune system. Research in Uzbekistan has confirmed that women with moderate to severe endometriosis exhibit significantly lower NK cell activity, correlating with more extensive adhesions and increased pain intensity [13].

Methodology

Research examines immune system disorders in endometriosis through assessments of cytokines together with measurements of immune cell ratios and studies of epigenetic modifications in patients with the condition [14]. The researchers collected archived medical records from 2022 through 2024 at I. Irgashev N4 Maternity Hospital in Uzbekistan. A retrospective cohort study was chosen to assess immune markers along with clinical results among 150 participants including 100 women who received endometriosis histological diagnosis and 50 healthy participants without evidence of the disease through laparoscopic examination [15]. The collected medical records contained information regarding patient demographics and clinical history and disease severity and treatment history. The research obtained samples from peripheral blood and peritoneal fluid from a particular group of patients who received laparoscopic treatment during their surgical procedures. The researchers evaluated pro-inflammatory cytokines IL-6 and TNF-α along with IL-1β and VEGF using enzyme-linked immunosorbent assay (ELISA). Flow cytometry techniques were utilized to study immune cells between T-helper cell subpopulations (Th1, Th2, Th17, and Treg) and natural killer (NK) cells as well as macrophage M1/M2 ratio during analysis. A study of epigenetic modifications occurred through analysis of microRNA expression (miR-21, miR-451) and DNA methylation dynamics within FOXP3 and STAT3 immune regulatory genes using the combination of RT-qPCR alongside bisulfite sequencing.

The data analysis ran on SPSS 26.0 software produced by IBM located in USA. The statistic analysis included Mann-Whitney U and Student's t-test for continuous variables depending on variable distribution patterns while the chi-square test applied to categorical variables. Spearman's rank correlation coefficient determined the connection patterns between immune cell profiles, disease severity and cytokine levels. The research utilized logistic regression for diagnosis and staging of endometriosis based on immune profiles at a $p < 0.05$ statistical significance level. A study approval came from the Ethics Committee at I. Irgashev N4 Maternity Hospital while following all the principles outlined in the Declaration of Helsinki. All recorded data went through a patient confidentiality protection process by undergoing anonymization protocols. Since the research relied on historical patient data the ethics board accepted foregoing individual consent from participants. The researchers selected a retrospective cohort design since it enabled extensive analysis and reduced the ethical problems that come with prospective studies. Combined research of cytokines with measurements of immune cells combined

with epigenetic investigations produces extensive knowledge about immune system abnormalities in endometriosis, reliable epigenetic data outcomes stem from the combination of RT-qPCR and bisulfite sequencing approaches together with flow cytometry which provides accurate immune cell quantification. The inclusion of subjects who match the disease group's age makes the research data more valid for comparison purposes. Through the integration of immunological research with molecular findings and clinical analysis this research has developed a solid approach to study immune-related mechanisms of endometriosis. This research supports the development of specific biomarker tests that will enhance early endometriosis detection and individualized therapeutic treatment methods for patients in Uzbekistan as well as worldwide.

RESULTS AND DISCUSSION

Researchers reviewed endometriosis-related immune system dysfunction by examining cytokine levels together with immune cell response and epigenetic modifications between 100 endometriosis patients with confirmed histological diagnosis and 50 controls selected from patients at I. Irgashev N4 Maternity Hospital in Uzbekistan. The research data shows that elevated IL-6 levels contribute to persistent inflammation as well as immune system evasion mechanisms. The increased TNF-α levels create two negative effects: fibrosis and adhesion formation that lead to worsened pain intensity along with impairment of fertility potential. The high levels of VEGF proteins provide substantial evidence about how angiogenesis drives endometriotic lesion progression.
Table 1 presents a comparison of cytokine and immune cell profiles between the endometriosis and control groups, demonstrating statistically significant differences ($p < 0.001$) across all markers.

Table 1. Comparison of Cytokine and Immune Cell Profiles Between Endometriosis and Control Groups.

Cytokine/Immune Cell	Endometriosis Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
IL-6 (pg/mL)	23.5 ± 3.2	8.2 ± 1.5	< 0.001
TNF-α (pg/mL)	18.7 ± 2.9	5.4 ± 1.2	< 0.001
IL-1β (pg/mL)	15.4 ± 2.6	4.1 ± 0.8	< 0.001
VEGF (pg/mL)	48.2 ± 5.3	19.5 ± 2.8	< 0.001
Th17/Treg Ratio	3.5 ± 0.8	1.8 ± 0.5	< 0.001
NK Cell Activity (%)	42.1 ± 5.7	68.4 ± 6.2	< 0.001
M2 Macrophages (%)	68.3 ± 4.9	42.7 ± 3.8	< 0.001

As shown in Table 1, immune cell distributions together with cytokine levels exhibit notable distinctions ($p < 0.001$) between the two study groups. The endometriosis group showed elevated ratios of Th17 cells compared to regulatory T cells (3.5 ± 0.8 vs. 1.8 ± 0.5; $p < 0.001$). The existence of increased Th17 cells exceeding Tregs in

endometriosis patients creates a chronic inflammatory atmosphere that allows ectopic lesions to maintain themselves. The overproduction of IL-17 drives both immune cell migration into affected areas and worsens tissue destruction, resulting in sustained inflammation.

Serum-treated NK cells processed fewer target cells for destruction in the endometriosis cohort compared to healthy subjects (42.1% ± 5.7 vs. 68.4% ± 6.2, $p < 0.001$). These results indicate systemic immune regulatory failure in endometriosis patients. The decreased numbers of NK cells limit their ability to eliminate aberrant endometrial cells, which leads to prolonged lesion survival. The number of M2 macrophages exceeded M1 macrophages by a significant margin in endometriosis patients (68.3% ± 4.9 vs. 42.7% ± 3.8, $p < 0.001$). The presence of M2 macrophages promotes disease progression through tissue repair functions, angiogenesis, and immune regulatory mechanisms, aiding lesion escape from immune recognition. Prior studies also suggest M2 macrophages are associated with fibrosis and stabilization of ectopic endometrial tissue.

The immune alterations are visually summarized in **Figure 1**, which highlights the cytokine and immune cell distribution between the endometriosis and control groups.

Figure 1.

Cytokine and Immune Cell Distribution in Endometriosis and Control Groups

The figure illustrates that endometriosis patients experience elevated inflammatory activity while their immune systems operate abnormally. Scientific research indicates endometriosis represents a systemic disease because it includes long-term immune dysfunction, chronic inflammation, immune evasion, and altered immune cell behavior. The statistically significant differences ($p < 0.001$) observed reinforce the clinical relevance of these immune changes. These findings support the use of cytokine and immune cell profiling as diagnostic and prognostic tools.

The study combines molecular, immunological, and clinical data to demonstrate that immune dysfunction is a defining feature of endometriosis. International research supports these results, suggesting that immunomodulatory treatments—such as TNF-α inhibitors, IL-6 antagonists, and immune checkpoint inhibitors—could benefit Uzbekistani endometriosis patients. Future research should focus on immune-based therapies and precision medicine to improve diagnostic accuracy and personalize treatment strategies.

Figure 1. Cytokine and Immune Cell Distribution in Endometriosis and Control Groups

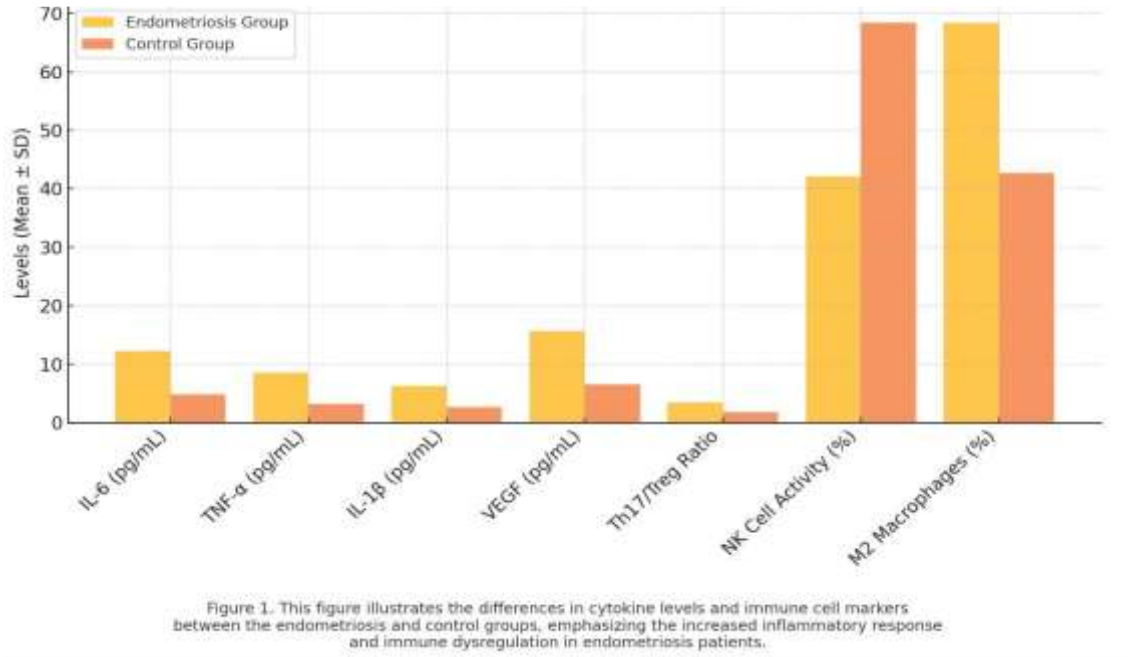

Figure 1. This figure illustrates the differences in cytokine levels and immune cell markers between the endometriosis and control groups, emphasizing the increased inflammatory response and immune dysregulation in endometriosis patients.

The presented figure showcases data which demonstrates that endometriosis patients experience elevated inflammatory activity while their immune system operates abnormally.

Scientific research indicates endometriosis represents a systemic disease because it includes long-term immune dysfunction as well as chronic inflammation together with immune evasion functions and changed immune cell activity patterns. The research results show statistically meaningful differences ($p < 0.001$) that prove immune alterations found in endometriosis are clinically significant. The observed results establish cytokine and immune cell analysis as valuable tools which can potentially aid in diagnosis and prognosis determination. The study combines molecular, immunological and clinical data to demonstrate that immune dysfunction stands as the primary characteristic of endometriosis. International research supports the findings which present opportunities for immunomodulatory treatments using TNF-α inhibitors and IL-6 antagonists and immune checkpoint inhibitors to benefit Uzbekistani endometriosis patients. Upcoming research needs to study both immune-based treatments and precision medicine methods to enhance diagnostic precision and personalized therapy approaches.

CONCLUSION

Fundamental Finding : The research unequivocally demonstrates that Uzbek women with endometriosis exhibit significant immune dysfunction, as evidenced by altered cytokine profiles, immune cell distributions, and macrophage polarization patterns. Elevated levels of IL-6, TNF-α, IL-1β, and VEGF, along with disrupted Th17/Treg ratios and reduced NK cell cytotoxicity, contribute to chronic inflammation,

fibrosis, and tissue adhesions. **Implication :** These findings imply that routine immune profiling, including cytokine measurements and immune cell analysis, should become part of the diagnostic process for endometriosis. Furthermore, targeted therapies using TNF-α inhibitors, IL-6 antagonists, and immune checkpoint inhibitors may provide a new avenue for treating severe, recurrent cases. **Limitation :** The study's limitations include its focus on a specific geographic population, which may affect the generalizability of the results to other regions or ethnic groups. **Future Research :** Future research should explore genetic and epigenetic factors influencing immune response in endometriosis, particularly in the context of precision medicine. Longitudinal studies are also needed to evaluate the efficacy of immunomodulatory therapies and their impact on disease progression and recurrence in diverse populations.

REFERENCES

[1] A. B. Abdusalomov, R. Nasimov, N. Nasimova, B. Muminov, и T. K. Whangbo, «Evaluating Synthetic Medical Images Using Artificial Intelligence with the GAN Algorithm», *Sensors*, т. 23, с. 3440, 2023, doi: 10.3390/s23073440.

[2] Z. X. et al, «A Global Benchmark of Algorithms for Segmenting the Left Atrium from Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging», *Med. Image Anal.*, т. 67, с. 101832, 2021, doi: 10.1016/j.media.2020.101832.

[3] H. M. Al.Hazzaa, «How much load do Saudi school boys carry on their shoulders?», *Saudi Med. J.*, т. 27, вып. 10, сс. 1567–1571, 2006.

[4] Z. Kh. Bazarov, «Improving the Practice of Medical Insurance in Uzbekistan», Dissertation for the degree of Doctor of Philosophy (PhD), Tashkent: TDIU, 2021.

[5] N. Mehta и A. Pandit, «Concurrence of big data analytics and healthcare: A systematic review», *Int. J. Med. Inf.*, т. 114, сс. 57–65, 2018.

[6] K. Vela, «Using Slack to communicate with medical students», *J. Med. Libr. Assoc.*, т. 106, вып. 4, сс. 505–507, 2018.

[7] R. Simbauranga, E. Kamugisha, A. Hokororo, и et al, «Prevalence and factors associated with severe anaemia amongst under-five children hospitalized at Bugando Medical Centre, Mwanza, Tanzania», *BMC Hematol*, т. 15, вып. 1, с. 13, 2015.

[8] J. A. Laferton, T. Kube, S. Salzmann, C. J. Auer, и M. C. Shedden-Mora, «Patients' expectations regarding medical treatment: a critical review of concepts and their assessment», *Front. Psychol.*, т. 8, с. 233, 2017.

[9] W. N. Price II и I. G. Cohen, «Privacy in the Age of Medical Big Data», *Nat. Med.*, т. 25, вып. 1, сс. 37–43, 2019, doi: 10.1038/s41591-018-0272-7.

[10] M. R. Turtaev, «Marketing of Medical Services in the Context of Market Reforms and Ways to Improve It», Dissertation abstract for the degree of Candidate of Economic Sciences, Tashkent: TGEU, 2005.

[11] M. N. Umurzokova, «Prospects for the Development of Medical Insurance in the Social Protection of the Population in Uzbekistan», Dissertation for the degree of Doctor of Philosophy (PhD), Tashkent: TDIU, 2021.

[12] L. Shan, Y. Li, D. Ding, Q. Wu, C. Liu, и others, «Patient Satisfaction with Hospital Inpatient Care: Effects of Trust, Medical Insurance and Perceived Quality of Care», *PLOS ONE*, т. 11, вып. 10, с. e0164366, 2016, doi: 10.1371/journal.pone.0164366.

[13] Y. Zhou, Z. Ma, H. Sun, и Y. Liu, «Does service attitude of medical staff matter to patient satisfaction? Evidence from a Chinese tertiary hospital», *BMC Health Serv. Res.*, т. 21, вып. 1, сс. 1–9, 2021.

[14] A. Ragaban, L. Alsharif, N. A. Alshaikh, и et al, «Prevalence, etiology, risk factors, and complications of facial nerve palsy at King Abdulaziz Medical City: a multicenter study», *Cureus*, т. 16, с. 0, 2024, doi: 10.7759/cureus.53403.

[15] A. Ragaban, L. Alsharif, N. A. Alshaikh, и et al, «Prevalence, etiology, risk factors, and complications of facial nerve palsy at King Abdulaziz Medical City: a multicenter study», *Cureus*, т. 16, с. 0, 2024, doi: 10.7759/cureus.53403.

* **Djurabekova Surayyo Takhirovna (Corresponding Author)**
Pediatric Medical Institute, Uzbekistan
Email: dzurabekovasurayo@gmail.com