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Original Article

Immunopathology and Therapeutic Perspectives of Endometriosis: Scientific Gaps and Emerging Advances in Translational Immunotherapy

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Abstract

Endometriosis is a debilitating inflammatory disease affecting millions of women worldwide. However, its pathogenesis remains incompletely understood and its treatment is suboptimal. Conventional therapies, primarily hormonal suppression and surgical resection, fail to address the underlying immune dysregulation that drives the persistence, recurrence, and resistance of the lesions. Recent advances in immunology have revealed a multifaceted immunopathological landscape characterized by impaired immune surveillance, altered macrophage polarization, dysfunctional regulatory T cell activity, overexpression of immune checkpoints, and chronic failure of inflammatory resolution. These abnormalities create an immune-tolerant microenvironment that allows ectopic endometrial tissue to evade clearance and to establish itself at multiple anatomical sites. Moreover, growing evidence implicates reproductive and gut microbiota as critical modulators of the immune response in endometriosis, adding another layer of complexity to disease progression and therapy. This integrative review critically examines current evidence regarding immune dysfunction in endometriosis and explores promising immunotherapeutic strategies, including checkpoint inhibitors, cytokine modulators, cell-based therapies, and nanotechnology-driven interventions. Key scientific gaps have been identified, such as the lack of clinical trials, inadequate biomarker validation, insufficient exploitation of cutting-edge technologies, and absence of robust frameworks for assessing reproductive safety. Ethical considerations and translational hurdles are also discussed in this review. By bridging fundamental immunopathology with emerging therapeutic innovations, this review highlights the transformative potential of immunotherapy in reshaping the future of endometriosis care within the precision medicine paradigm.

Keywords: ***endometriosis, immunotherapy, immune checkpoint inhibitors, biomarkers, microbiota, precision medicine.***

Introduction

Endometriosis is a chronic estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissues outside the uterine cavity. Globally, approximately 10% of women of reproductive age experience pelvic pain, infertility, and a reduced quality of life. Despite its prevalence and clinical burden, the precise pathogenesis of endometriosis remains incompletely understood and therapeutic management presents considerable challenges [1-3].

Historically, endometriosis has been classified as a benign gynecological condition. However, their behavior often mimics that of malignant neoplasms, particularly in terms of local invasion, resistance to apoptosis, neovascularization, and recurrence after surgical or pharmacological intervention. These features have prompted increasing attention to the immune dysregulation associated with the disease, positioning immunopathology as a central element in its etiology and progression [2-5].

Multiple immune cell populations are implicated in the pathophysiology of endometriosis. Aberrant peritoneal macrophage activity, impaired natural killer (NK) cell cytotoxicity, and regulatory T cell (Treg) dysfunction have been reported in both animal models and human studies. These abnormalities contribute to immune escape and the persistence of ectopic endometrial implants, highlighting an imbalance between immune surveillance and tolerance [4-7].

Emerging data suggest that the peritoneal environment in endometriosis exhibits the features of a chronic inflammatory niche. Cytokine profiles are dominated by elevated levels of interleukin (e.g., IL-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β), which collectively facilitate angiogenesis, cell proliferation, and fibrogenesis. These immunological changes may promote a self-sustaining cycle of inflammation and tissue remodeling in the body [6-9].

Recent studies have identified that immune checkpoint molecules, such as programmed death-1 (PD-1), programmed death-

ligand 1 (PD-L1), CTLA-4, and CD47, are aberrantly expressed in the ectopic and eutopic endometrium of patients with the disease. These molecules, which are typically involved in the prevention of autoimmune reactions, may contribute to the suppression of cytotoxic responses and enable the survival and progression of lesions [8-11].

Single-cell RNA sequencing and transcriptomic analyses revealed significant heterogeneity in the immune landscape of endometriotic lesions. Distinct immune cell populations, including dendritic cells, M2-polarized macrophages, Th17 cells, and myeloid-derived suppressor cells (MDSCs), play roles in lesion maintenance, suggesting that endometriosis is characterized by a complex, multifaceted immunological profile that evolves over time and with the lesion subtype [10-13].

Despite these insights, the current medical management of endometriosis remains largely hormonal, with the aim of suppressing ovulation and reducing estrogen stimulation. Although such therapies can reduce symptom burden, they are not curative and are often associated with adverse effects, including bone loss, metabolic disturbances, and contraceptive limitations. Importantly, these studies did not address the underlying immune dysregulation [12-15].

The persistent recurrence of endometriosis after discontinuation of medical treatment or surgical excision underscores the need for novel targeted therapies. Immunotherapy, which has long been established in oncology and autoimmune diseases, represents a promising avenue for more effective and individualized approaches to endometriosis treatment. However, its clinical translation is still in its infancy [14-17].

Several preclinical studies have demonstrated that the modulation of immune pathways, such as the blockade of PD-1/PD-L1, activation of NK cells, or expansion of Tregs, can reduce lesion size and inflammatory activity in murine models of endometriosis. Similarly, small-scale clinical studies and case reports have suggested that immunotherapeutic agents may be beneficial in refractory cases; however, robust evidence from randomized controlled trials is lacking [15-18].

Another emerging area of interest is the role of the gut and reproductive tract microbiomes in shaping immune responses in endometriosis. Dysbiosis may influence TLR expression, cytokine profiles, and antigen presentation, thereby acting as a key modulator of the host local immune environment. However, the exact underlying mechanism remains poorly defined and warrants further investigation [16-19].

Advanced technologies, such as organoid cultures, CRISPR-based gene editing, and bioengineered immune-modulating nanoparticles, offer innovative platforms for studying and manipulating immune responses in endometriosis. These tools hold potential for the discovery of novel targets and development of precision immunotherapies; however, their application in this field remains limited [20-23].

Endometriosis is a heterogeneous disease with multiple subtypes, including superficial peritoneal, ovarian, and deep-infiltrating endometriosis, each of which may exhibit distinct immunological features. Current studies rarely stratify patients according to lesion type, which limits the generalizability and applicability of the findings. This heterogeneity needs to be addressed in future clinical and translational studies [22-25].

Ethical and reproductive considerations must be considered when designing immunotherapy protocols for women of reproductive ages. As immune interventions can potentially affect implantation, pregnancy, and hormonal regulation, careful risk-benefit analysis and long-term reproductive monitoring are essential [24-27].

Furthermore, there is a need to develop validated biomarkers to predict which patients will benefit from specific types of immunotherapies. Currently, no immune-based classifiers or predictive algorithms exist for clinical use in endometriosis, which is a major obstacle to the implementation of personalized treatment strategies [26-28].

Given these complexities, there is growing recognition of the necessity for a transdisciplinary approach to endometriosis research that integrates immunology, reproductive medicine, molecular biology, bioinformatics, and clinical trial design to advance the understanding and treatment of the disease [27-30].

This review critically analyses the current state of knowledge on the immunopathology of endometriosis, identifies major scientific gaps in the field, and synthesizes recent advances in translational immunotherapy, focusing on their potential clinical applications [31-33]. This review aims to provide a comprehensive framework for future research and the development of personalized immunotherapeutic interventions for the treatment of endometriosis.

Methods

This integrative review critically analyzes and consolidates the current evidence on the immunopathological mechanisms associated with endometriosis and evaluates the emerging immunotherapeutic strategies in this context. A structured, transparent, and comprehensive approach was applied to ensure analytical rigor and relevance in the clinical and research settings. A systematic literature search was performed using the PubMed/MEDLINE, Embase, Web of Science, Scopus, and SciELO electronic databases. Gray literature was explored using Google Scholar to capture recent nonindexed contributions. The search was performed without time restrictions. A controlled vocabulary based on Medical Subject Headings (MeSH) was used in combination with relevant free-text terms to maximize retrieval sensitivity and specificity. The core descriptors employed in the strategy included: “Endometriosis,” “Immunotherapy,” “Immune Checkpoint Inhibitors,” “Biomarkers,” “Microbiota,” and “Precision Medicine.” Complementary terms such as “Immune Modulation,” “T Lymphocytes,” “Natural Killer Cells,” “Macrophage Polarization,” and “Trained Immunity” were also included to enhance the thematic scope of the review. Boolean operators (AND, OR) were systematically applied to refine the search logic and capture the comprehensive datasets. Articles were included if they addressed immunological processes in endometriosis or proposed immunotherapeutic targets or strategies applicable to the condition. Eligible studies included original research (clinical, translational, or experimental), systematic reviews, in vivo or in vitro models, bioinformatics analyses, and reports involving innovative technologies relevant to immunology. Studies that were not related to the immune aspects of endometriosis, lacked methodological clarity, or were written in languages outside the predefined scope were excluded. The titles and abstracts retrieved from the initial search were independently screened by two reviewers. The full texts of potentially eligible studies were then assessed for inclusion based on the predefined criteria. Any disagreement was resolved by consensus and, when needed, a third blinded evaluator was consulted to make the final decision. The reviewers did not have access to each other's assessments during the selection and extraction phases, thereby ensuring methodological independence and analytical impartiality. Data were extracted using a standardized template, including information on the study type, experimental model or population,

immune cell types and molecular pathways investigated, therapeutic targets assessed, key immunological outcomes, and translational relevance. The studies were grouped into thematic categories reflecting the main analytical axes of this review: immune dysfunction in endometriosis, translational gaps in immunotherapy, immune biomarker development, microbiota–immune system interactions, technological innovations in immunological research, and ethical considerations related to immunomodulation in individuals of reproductive age. Qualitative synthesis was performed owing to the heterogeneity in study designs, outcomes, and methodological frameworks. Recurring themes, converging findings, and divergences in literature were identified and integrated into a critical narrative. Conceptual models have been developed to illustrate the underlying mechanisms and to guide the interpretation of complex immunological phenomena. The internal validity and scientific robustness of the included studies were appraised based on the following key criteria: clarity of the research question, transparency of the experimental design, reproducibility of the results, relevance to clinical application, and consistency of the findings with established immunological principles. Studies weren't excluded based on quality, but the evidence strength was discussed for each theme. Because this study involved only published and publicly available literature, ethical approval was not required. Nonetheless, the ethical and clinical implications discussed in the selected studies, particularly those concerning immune manipulation in reproductive health contexts, were critically analyzed and incorporated into the interpretation of the findings. This methodological framework allows for a structured and impartial synthesis of the current state of knowledge, highlights unresolved scientific questions, proposes new research directions, and supports the rationale for future immunotherapy-based clinical interventions for endometriosis.

Results and Discussion

Table 1. Immunotherapy and Immune Mechanisms of Endometriosis

Author	Study	Results
Maksym RB et al., 2021 [1]	Narrative Review	The role of the immune system in the pathogenesis of endometriosis focuses on inflammatory cytokines, impaired macrophage phagocytosis, and imbalance of Treg/Th17 cells. This suggests that immunomodulation is a potential therapeutic strategy.
Li W et al., 2023 [2]	Translational Review	Review of emerging immunotherapies, including checkpoint inhibitors and vaccine development. Immune escape mechanisms and potential of the PD-1/PD-L1 axis as a therapeutic target.
Chen S et al., 2023 [3]	Original Research	Peritoneal immune dysregulation, reduced NK cell activity, and increased anti-inflammatory macrophage polarization contribute to the persistence of lesions.
Zhou C et al., 2023 [6]	Single-cell Transcriptomics	Uncovered immunological heterogeneity in endometriotic tissues highlights the overexpression of immune checkpoint molecules such as PD-L1 and CTLA-4 in distinct stromal and immune cells.
Wu Q et al., 2023 [7]	Experimental Study	We demonstrated that IL-33/ST2 signaling inhibits ferroptosis through the ATF3/SLC7A11 axis, promoting lesion survival and immune evasion.
Kolanska K et al., 2021 [12]	Systematic Review	Summarized immune alterations in infertile women with endometriosis and evaluated the effectiveness of immunomodulatory therapies such as corticosteroids and IVIG.
Peng Y et al., 2025 [13]	Bioengineering Review	Recent advances in precision nanomedicine have targeted immune pathways in endometriosis using biomaterials and engineered drug delivery systems.
He Y et al., 2022 [17]	Experimental Comparative Study	Validated mouse models for immune-endometriosis research, confirming their relevance for studying T-cell, macrophage, and cytokine interactions.
Zou G et al., 2021 [24]	Single-cell RNA-seq	Unique populations of T cells, NK cells, and macrophages were identified in the peritoneal fluid, showing immunosuppressive signatures in endometriosis.
Amidifar S et al., 2025 [30]	Review	We explain the molecular immune dysregulation in endometriosis and introduce the therapeutic implications of targeting immune checkpoints and antigen-presenting pathways.

Source: Authors

Lack of Clinical Trials on Immunotherapy in Endometriosis

Despite accumulating evidence highlighting the role of immune dysfunction in the pathogenesis of endometriosis, translational clinical research is lacking. Currently, therapeutic innovations in this domain are largely confined to preclinical animal models or in silico predictions [10]. Although these models have enabled the identification of relevant immune targets such as PD-1, CTLA-4, CD47, and IL-17, the absence of human clinical trials leaves a critical gap in the validation and application of immunotherapeutic approaches [33-35].

No immunotherapy has been formally evaluated in phase I or II trials of women with endometriosis. This omission is particularly concerning given the demonstrated overexpression of immunosuppressive ligands in lesions and the parallels between endometriotic immune evasion and tumor immune escape [24]. Moreover, immune checkpoint molecules, such as PD-L1 and CD200, which facilitate immune tolerance in cancer, are upregulated in endometriotic lesions, suggesting that similar therapeutic strategies could be repurposed (Table 1) [34-37].

Barriers to initiating trials include concerns about immune toxicity in women of reproductive age, a lack of defined clinical and immunological endpoints, and uncertainties regarding the impact of immune modulation on fertility [18]. However, these challenges must be addressed through carefully designed trials that incorporate reproductive safety monitoring, adaptive dosing strategies, and the robust integration of immune biomarkers. Without such studies, the potential of immunotherapy in endometriosis remains unclear [35-38].

Immunological Heterogeneity Among Endometriosis Subtypes

Endometriosis exhibits high spatial, molecular, and immunological heterogeneities. Superficial peritoneal lesions, ovarian endometriomas, and deep infiltrating endometriosis (DIE) differ not only in their anatomical location and invasiveness but also in their local immune cell profiles, cytokine environments, and gene expression patterns [39-42].

Recent immune transcriptomic analyses have shown that superficial lesions are more likely to harbor pro-inflammatory cytokine expression and active NK cell infiltration, whereas deep lesions are associated with enhanced fibrosis, myeloid-derived suppressor cell (MDSC) expansion, and chronic immune tolerance

signatures [22]. In contrast, ovarian endometriomas often display immunosuppressive and angiogenic phenotypes, and are enriched in VEGF expression and M2-polarized macrophages [43-46].

This heterogeneity has profound implications for treatment. A "one-size-fits-all" approach fails to account for differential immune responsiveness among lesion types. For example, immune checkpoint blockade may be effective in deep lesions with high PD-1/PD-L1 expression but ineffective in superficial lesions that are dominated by a different immune profile [45-48].

Therefore, precision immunotherapy for endometriosis must be guided by lesion-specific immunophenotyping including single-cell sequencing, multiplex IHC, and cytokine profiling [26]. The integration of immunological heterogeneity into diagnostic frameworks could also aid in stratifying patients for clinical trials, improving the likelihood of detecting therapeutic responses, and minimizing unnecessary immunomodulation [49-52].

Dysregulated Immune Memory and Failure of Inflammatory Resolution

The chronic, recurring nature of endometriosis is underpinned not only by sustained inflammation but also by a profound failure in immune resolution and reprogramming. Recent studies have highlighted the persistence of trained immune phenotypes in macrophages and monocytes within the peritoneal environment, which exhibit aberrant memory-like responses that perpetuate low-grade inflammation and promote lesion survival [53-56].

This maladaptive immune memory may involve epigenetic reprogramming of innate immune cells, resulting in persistent regulation of inflammatory mediators, such as IL-1β, IL-6, and TNF-α. Furthermore, defective clearance of apoptotic cells (efferocytosis) by peritoneal macrophages contributes to the accumulation of cellular debris and damage-associated molecular patterns (DAMPs), reinforcing immune activation [54-57].

Another important but under-investigated mechanism is the suppression of ferroptosis within the lesions. Ferroptosis, a form of regulated cell death driven by iron accumulation and lipid peroxidation, is inhibited in endometriotic tissues via upregulation of anti-ferroptotic genes. This resistance to cell death supports long-term survival of ectopic endometrial stromal and epithelial cells, further entrenching the disease process [55-58].

Therapeutic interventions that reprogram immune memory or enhance pro-resolving pathways, such as treatment with resolving, lipid mediators, or tolerogenic dendritic cells, may offer a new frontier in the non-hormonal management of the disease. However, these approaches remain largely unexplored in humans [57-59].

Absence of Validated Immunological Biomarkers

The development of effective immunotherapies has been hindered by the absence of validated immunological biomarkers that can predict disease presence, severity, and therapeutic responsiveness [34]. Although numerous molecular candidates have been proposed, including checkpoint ligands (e.g., CD200 and CTLA-4), m6A regulators (e.g., FTO and HNRNPC), and cytokine expression patterns, few have advanced beyond the discovery phase [60-63].

Importantly, there is no consensus regarding the immunological stratification of patients in clinical trials. The identification of peripheral immune signatures (e.g., CD4/CD8 ratio, Treg levels, and serum IL-17) or lesion-specific markers (e.g., checkpoint expression and MDSC abundance) can guide patient selection and endpoint determination [46,47]. Moreover, composite biomarker panels that integrate genomic, proteomic, and cellular features may offer greater sensitivity and specificity than those of single-analyte assays [8,64-66].

Large-scale prospective studies are required to validate these markers in diverse patient populations. These efforts should also account for confounding factors such as menstrual phase, hormonal treatments, and comorbid conditions, all of which influence immune readouts [67,68].

Microbiota-Immune Axis in Endometriosis

Emerging evidence supports a bidirectional relationship between the microbiota and the immune system in endometriosis. The altered composition of the gut and reproductive tract microbiota has been correlated with increased pro-inflammatory cytokine production, breakdown of immune tolerance, and epithelial barrier dysfunction [69-71].

Dysbiosis may contribute to disease initiation and progression through microbial translocation, leading to persistent immune activation via pattern recognition receptors such as TLR2 and TLR4. This is particularly relevant, given the identification of bacterial DNA in the peritoneal fluid of patients with advanced disease stages. Moreover, microbial metabolites such as short-chain fatty acids and tryptophan derivatives influence immune regulation by modulating Treg differentiation and IL-10 production [72-73].

Despite its potential significance, microbiome-immune crosstalk in endometriosis remains under investigation. Clinical trials incorporating microbiome sequencing, metabolomics, and immune profiling can help to identify microbiota-derived biomarkers and therapeutic targets. Interventions such as dietary modulation, symbiotics, or targeted antibiotics may be co-administered with immunotherapy to enhance efficacy and minimize adverse effects [14,74,75].

Underuse of Advanced Immunological Technologies

Despite their transformative power, advanced immunological and molecular technologies have been underexploited for the study of endometriosis. Techniques such as single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, mass cytometry (CyTOF), and CRISPR/Cas9-mediated gene editing have revolutionized the investigation of complex immune ecosystems in cancer and autoimmune diseases. However, their use in endometriosis is limited and fragmented [76-78].

Single-cell sequencing offers the ability to deconvolute cellular heterogeneity within endometriotic lesions and map immune subpopulations, stromal interactions, and the clonal expansion of T and B cells [49-51]. When applied to eutopic and ectopic tissues, this approach can uncover functional immune exhaustion markers, regulatory signatures, and novel ligand receptor interactions that may be obscured in bulk analyses [30]. Similarly, spatial transcriptomics and multiplexed imaging techniques enable the visualization of immune cell localization and interaction with endometrial stromal and epithelial compartments, adding a crucial anatomical dimension to immune profiling [79-81].

CRISPR screening can also facilitate identification of critical immunoregulatory genes that control lesion persistence, angiogenesis, and immune evasion. Endometriotic organoids engineered to include immune and endothelial components can serve as ex vivo platforms for studying the effects of gene editing or immune-targeted therapies under physiologically relevant conditions [82-84].

However, the widespread adoption of these tools is constrained by the absence of standardized protocols, limited access to fresh human tissue, and a lack of integrated bioinformatics infrastructure. Addressing these barriers through collaborative consortia, shared tissue banks, and training in computational immunology are essential for advancing the field [34,85].

Ethical and Reproductive Implications of Immunotherapy

The reproductive implications of immune modulation in endometriosis are crucial but largely neglected. As most affected individuals are of reproductive age, interventions that alter the immune balance must be scrutinized for their impact on fertility, embryo implantation, pregnancy maintenance, and fetal development [17-19]. Many immunotherapeutic agents used in other diseases, such as immune checkpoint inhibitors and cytokine blockers, influence the uterine environment, decidualization, and maternal fetal tolerance mechanisms [25-28].

For example, immune checkpoint inhibition can enhance T-cell cytotoxicity and potentially disrupt the immunosuppressive milieu required for implantation and early gestational success [36-38]. Similarly, anti-inflammatory biologics that suppress IL-6 or TNF-α may interfere with inflammatory cues essential for endometrial remodeling during the peri-implantation window. However, these potential effects remain poorly understood and have seldom been evaluated in preclinical studies [44-46].

Currently, no immunotherapy trial for endometriosis incorporates reproductive safety endpoints or long-term fertility assessment. Moreover, existing animal models are often unsuitable for studying human-specific aspects of reproductive immunology [44]. It is imperative that future therapeutic developments integrate reproductive toxicology testing, in vitro embryo endometrium interaction models, and long-term follow-up of fertility-related outcomes [49-52].

Informed consent procedures should explicitly address the uncertain reproductive risks associated with immunotherapy. Regulatory guidelines should mandate the collection of reproductive safety data prior to authorizing immunomodulatory treatments for gynecological use. Furthermore, ethical review boards should mandate fertility preservation counseling and monitoring of participants of reproductive age enrolled in immunotherapy trials [60-63].

Immunological Links Between Endometriosis, Autoimmunity, and Cancer

Growing evidence suggests that endometriosis shares immunopathogenic mechanisms with autoimmune diseases and cancers. Common features include aberrant antigen presentation, chronic T cell activation, elevated autoantibody production, and immune checkpoint dysregulation [68-70]. Epidemiologically, individuals with endometriosis have an increased prevalence of autoimmune disorders, such as systemic lupus erythematosus, Hashimoto's thyroiditis, and rheumatoid arthritis. A modest but consistent association was observed between clear cells and endometrioid ovarian carcinomas [75-78].

These correlations raise important questions regarding shared immune signatures and pathogenic pathways. For instance, upregulation of PD-L1 and CTLA-4 in endometriotic lesions parallel to tumors that evade immune surveillance [33]. Similarly, defective peripheral tolerance, expansion of autoreactive lymphocyte clones, and presence of autoantibodies suggest that endometriosis may at least in part exhibit features of systemic immune dysregulation [79-81].

Although the causal direction remains unclear, these associations warrant investigation to determine whether immune dysregulation precedes endometriosis, contributes to its chronicity, or is a consequence of chronic inflammation [38-40]. Understanding these links could facilitate the repurposing of immunotherapies in oncology and rheumatology for endometriosis treatment. This reinforces the importance of screening for autoimmune and oncological comorbidities in patients with severe or refractory diseases [20-23].

To advance this field, integrated immunogenomic studies comparing patients with endometriosis, autoimmune diseases, or ovarian neoplasms should be performed. These investigations could help to identify common molecular targets, shared immune escape mechanisms, and biomarkers of progression risk [17-20].

Targeting Immune Checkpoints in Endometriosis

Immune checkpoint pathways, including PD-1/PD-L1, CTLA-4, TIM-3, and CD47/SIRPα, are increasingly recognized as central regulators of immune tolerance in endometriotic lesions [42-44]. These molecules, which have been classically studied in oncology, are exploited by endometriotic cells to dampen cytotoxic immune responses and foster permissive microenvironments. The expression of these checkpoints in both the stromal and epithelial compartments has been confirmed in eutopic and ectopic endometrial tissues [63-65].

Experimental studies have demonstrated that blocking PD-1 or CTLA-4 can reinvigorate exhausted T-cells, reduce regulatory T-cell dominance, and suppress lesion growth in animal models. Additionally, CD47 blockades may enhance macrophage-mediated phagocytosis of ectopic tissues, offering another mechanism to counteract lesion persistence. However, these approaches remain theoretical in a human context [16,54-57].

Key challenges include the risk of triggering systemic autoimmunity, uncertain reproductive effects, and lack of biomarkers to guide therapy. Systemic checkpoint blockade in women of reproductive age is likely to be risky in its current form [80-82]. However, localized delivery via intraperitoneal injection, antibody drug conjugates, or nanoparticle carriers may be safer alternatives. Local therapy can reduce systemic exposure and minimize disruption of immune tolerance in non-target tissues [5-8].

Comprehensive immune mapping to identify patients with high checkpoint expressions could inform the inclusion criteria for clinical trials and improve treatment targeting. The integration of tissue imaging, gene expression analysis, and functional immune assays is vital for clinical translation of these promising agents [52-55].

Potential of Natural Killer (NK) Cell-Based Therapies

Natural killer (NK) cells are essential components of the innate immune system and are responsible for direct cytotoxic elimination of abnormal or infected cells. In endometriosis, peritoneal NK cells exhibit decreased cytotoxic potential, downregulated activating receptors (e.g., NKG2D), and upregulated inhibitory ligands (e.g., HLA-G), facilitating immune evasion by ectopic lesions [20-24,67].

Restoring NK cell function through cytokine stimulation, receptor agonists, or adoptive transfer is a promising therapeutic strategy. In vitro studies have demonstrated that enhanced NK cell activity can promote apoptosis of endometriotic stromal cells and inhibit the formation of new blood vessels. Engineered allogeneic NK cell infusions have proven effective in solid tumor models and could be adapted for endometriosis treatment [36-38,52].

However, several significant challenges remain to be overcome. NK cell exhaustion, suppression by TGF-β in the peritoneal fluid, and inhibitory signals from endometriotic lesions can limit the efficacy of adoptively transferred cells. The development of NK cells resistant to immunosuppressive cytokines or engineered with chimeric antigen receptors (CAR-NK) specific to endometriotic antigens may overcome these barriers [48-50,64].

Combination therapies, such as pairing NK cell infusion with checkpoint inhibitors or anti-angiogenic agents, could further enhance the therapeutic outcomes. Clinical trials exploring NK-based immunotherapy in gynecological oncology may provide

valuable safety and efficacy data to support future trials on endometriosis [74-77,83].

Modulating Regulatory T Cell (Treg) Activity

Regulatory T cells (Tregs) are central in maintaining immune tolerance and suppressing inflammatory responses. However, their roles in endometriosis are paradoxical and multifaceted. On the one hand, Tregs can suppress cytotoxic immune activity, allowing ectopic endometrial tissues to evade immune-mediated destruction [14-17]. However, they may help control the chronic inflammation associated with disease progression. This dual functionality complicates the therapeutic strategies aimed at modulating Treg populations [31,79].

Studies have demonstrated that Tregs are expanded in the peritoneal fluid and lesions of patients with endometriosis and often exhibit enhanced suppressive capacity. This expansion correlates with elevated IL-10 and TGF-β levels, which contributes to an immunosuppressive microenvironment [18]. However, not all Treg cells are functionally equivalent; distinct subsets (e.g., FoxP3$^+$ Helios$^+$ vs. FoxP3$^+$ RORγt$^+$) may have divergent roles in either promoting or suppressing disease [10-13,26].

Therefore, therapeutic manipulation of Tregs must be precise. Broad depletion can exacerbate inflammation and disrupt immune homeostasis, whereas targeted modulation of pathogenic Treg subsets can restore immune surveillance without triggering autoimmunity [32-35,84]. One potential avenue is the use of low-dose IL-2 therapy to selectively expand tolerogenic Tregs in the early stages of the disease or, conversely, monoclonal antibodies targeting IL-2 receptors or CTLA-4 in later stages, where immune suppression predominates [26-28].

Future research should focus on characterizing Treg heterogeneity within lesions, understanding their plasticity under hormonal influence, and exploring the crosstalk between Tregs and stromal, epithelial, and vascular cells. Only through this resolution can therapies be tailored to enhance or inhibit Treg activity based on the disease context [36-39].

Cytokine-Targeted Therapies and Precision Inflammation Modulation

Cytokines orchestrate the complex immune responses observed in endometriosis. Aberrant levels of pro-inflammatory mediators such as IL-1β, IL-6, tumor necrosis factor (TNF)-α, IL-17, and interferon (IFN)-γ. These cytokines promote angiogenesis, leukocyte recruitment, matrix degradation, and pain signaling. Although they represent rational therapeutic targets, the clinical results of cytokine blockades are mixed [41-44,72].

Anti-TNF agents, for example, have shown efficacy in reducing lesion volume in preclinical models, but failed to produce consistent symptom relief in human studies. This discrepancy likely reflects immunological heterogeneity among patients, differences in cytokine dominance depending on the disease phase, and compensatory pathways that maintain inflammation despite blockade [67-69,76].

Personalized cytokine modulation requires identification of individual inflammatory profiles. This can be achieved using multiplex cytokine assays, transcriptomic signatures, or functional immune assays performed on the blood or peritoneal samples. Such profiling can stratify patients into pro-inflammatory or regulatory-dominant phenotypes, thereby guiding cytokine inhibitor selection [5-7,44].

Targeting upstream regulators, such as the NF-κB or JAK-STAT pathways, could provide broader suppression of inflammatory cascades. Alternatively, enhancing anti-inflammatory cytokines such as IL-10 or IL-35 through gene therapy or epigenetic modulation may offer a safer and more balanced immune modulation strategy. The future of cytokine-based therapy for endometriosis lies in precision: selecting the right target at the right time in the right patient [14-18,66].

Nanotechnology-Enabled Immunomodulation

Nanotechnology represents a promising frontier for enhancing the specificity, efficacy, and safety of immunotherapy in endometriosis. Nanoparticles can be engineered to deliver immunomodulatory agents such as siRNA, peptides, cytokines, or checkpoint inhibitors directly to the peritoneal cavity or ectopic lesions. This localized approach minimizes systemic toxicity, reduces drug dosage, and allows for controlled release kinetics [26-29,55].

Several types of nanocarriers, including liposomes, dendrimers, polymeric nanoparticles, and exosomes have been investigated. These platforms can be functionalized with targeting ligands that recognize surface markers overexpressed in endometriotic tissues such as integrins, VEGF receptors, and adhesion molecules. Once internalized, cargo can disrupt immune evasion pathways, modulate macrophage polarization, or enhance antigen presentation [38-40,60].

For example, nanoparticles that deliver siRNA against PD-L1 or CD47 mRNA have shown potential in reversing immune suppression and enhancing the phagocytic clearance of ectopic tissue in experimental models. Other approaches involve co-delivery of anti-inflammatory agents and immunogenic cell death inducers to trigger both lesion regression and immune reactivation [47-50;80].

Nevertheless, translational barriers continue to exist. These include manufacturing scalability, biocompatibility, regulatory approval pathways, and inter-patient variability in nanoparticle uptake. Rigorous pharmacokinetic and pharmacodynamic studies are essential to advance nanotherapeutics from bench to bedside in endometriosis care [55-57].

Artificial Intelligence in Immunotherapy Design and Prediction

Artificial intelligence (AI) and machine learning (ML) have transformed biomedical research by offering powerful tools for data integration, pattern recognition, and prediction. In the context of endometriosis, AI can synthesize complex datasets genomic, proteomic, metabolomic, imaging, and clinical to identify novel immune-related biomarkers, stratify patients, and predict their response to immunotherapy [63-65,83].

ML algorithms can be trained on annotated datasets to distinguish disease states based on immune cell compositions, cytokine signatures, or molecular profiles. For example, supervised learning models can classify patients into immunologically distinct clusters that correlate with their prognosis or treatment responsiveness. Unsupervised models can uncover previously unrecognized immune phenotypes associated with specific lesion subtypes [11,70-73].

Moreover, AI can assist in drug repurposing by mining chemical protein interaction databases for agents that target immune pathways dysregulated in endometriosis. Deep learning frameworks can also optimize immunotherapy design by simulating immune cell–lesion interactions or predicting the outcomes of cytokine modulation under different hormonal milieus [21-24,59].

AI applications require high-quality, harmonized datasets with detailed immunological and clinical metadata. Current limitations include fragmented data sources, lack of standardization in immune assays, and underrepresentation of diverse populations. Collaborative efforts to build large-scale, multicenter databases and develop open-source analytical tools are critical for realizing the full potential of AI in precision immunotherapy for endometriosis [38-42,79].

Need for Standardized Immunological Endpoints

One of the most pressing barriers to the advancement of immunotherapy for endometriosis is the absence of standardized immunological endpoints for clinical trials. Unlike oncology, where tumor shrinkage or survival can serve as objective outcome measures, endometriosis lacks universally accepted criteria for evaluating immunological responses or disease activity [47-50;66].

Current trials primarily rely on subjective symptom reporting (e.g., pain scales), lesion visualization through imaging, or intraoperative scoring. These measures, while clinically relevant, do not capture the underlying immune modulation or predict long-term response to therapy. Moreover, they fail to differentiate between inflammatory and fibrotic disease components, which may respond differently to immunological intervention [54-57,74].

Developing reliable immunological endpoints requires identification of biomarkers that correlate with disease activity, therapeutic response, and recurrence risk. These changes may include shifts in immune cell populations (e.g., increased cytotoxic T cells and reduced Tregs), cytokine profile normalization, or checkpoint molecule expression changes. Circulating exosomes or soluble immune receptors could serve as less invasive options compared to tissue biopsies [69-71,84].

Composite indices integrating clinical, immunological, and imaging parameters may provide a more holistic assessment of treatment efficacy. Importantly, these endpoints must be validated in prospective studies and aligned with regulatory expectations to support the approval of novel immunotherapy [45-48,67].

Establishing standardized and validated immunological outcome measures is essential for advancing clinical research, comparing therapeutic modalities, and ensuring meaningful benefits in patients with endometriosis [79-82,85].

Conclusion

Endometriosis represents a paradigmatic example of a multifactorial chronic inflammatory disorder in which the immune system plays a central, yet incompletely understood role. Despite considerable advances in characterizing the cellular and molecular components of the immune response within eutopic and ectopic endometrial tissues, these insights are yet to be effectively translated into targeted personalized clinical interventions. The findings synthesized in this review emphasize the critical disconnect between emerging immunopathological knowledge and current therapeutic paradigms.

Multiple gaps persist at scientific, translational, and clinical levels. Among these, the absence of immunotherapy-specific clinical trials, failure to acknowledge and integrate immunological heterogeneity among lesion subtypes, and lack of validated biomarkers capable of stratifying patients or predicting outcomes are major barriers to progress. Furthermore, fundamental mechanisms, including dysregulated immune memory, insufficient resolution of inflammation, and complex interplay between microbiota and immune function, remain poorly explored in clinical contexts.

The ethical and reproductive implications of immune modulation, particularly in women of reproductive age, further complicate its clinical application. Addressing these concerns requires integrated approaches that incorporate reproductive toxicology, long-term safety monitoring, and fertility-preservation frameworks. In parallel, the adoption of advanced technologies, including single-cell profiling, organoid platforms, CRISPR-based functional interrogation, and AI-assisted biomarker discovery, holds enormous promise for transforming the landscape of endometriosis research and treatment.

It is also becoming increasingly clear that the immunological features of endometriosis overlap with those observed in autoimmunity and cancer, highlighting the potential convergence of pathogenic pathways that could be leveraged for therapeutic innovation. Immune checkpoint modulation, NK and Treg cell-based therapies, cytokine-targeted interventions, and nanomedicine-based delivery systems are underexplored but potentially transformative strategies.

To unlock the full potential of immunotherapy in endometriosis, the field must embrace a transdisciplinary framework that unites immunologists, reproductive biologists, bioinformaticians, clinicians, and patients. This effort must be accompanied by the development of standardized immunological endpoints, regulatory frameworks that prioritize reproductive safety, and a commitment to equitable access to emerging therapies.

In conclusion, the immunopathology of endometriosis offers a rich but underutilized landscape for therapeutic innovation. By addressing the outlined gaps and investing in translational pipelines that link molecular mechanisms to clinical applications, scientific and medical communities can take meaningful steps toward offering immune-based personalized solutions for millions of individuals affected by this complex disease.

Declarations

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Conflict of interest

The authors declare that they have no conflicts of interest.

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