STM JOURNALS

Research & Reviews: A Journal of
Pharmacology

https://journals.stmjournals.com/rrjop

ISSN: 2230-9861 (Online)
ISSN: 2349-1299 (Print)
Volume 16, Issue 1, 2026
January–April
DOI (Journal): 10.37591/RRJoP

Review RRJOP

Immune Dysregulation and Cytokine Circuitry in Genital Endometriosis: Mechanistic Insights and Next-Generation Immunotherapeutic Strategies

Yadav Laxmi[1], Shubham Singh[2,*], Sanjesh Rathi[3]

Abstract

Genital endometriosis is increasingly recognized as an immune-mediated inflammatory disorder driven by complex interactions between dysregulated immune cells, cytokine hubs, and microbiome-derived modulators. This review introduces a novel "immune–cytokine circuitry" framework that unifies innate and adaptive immune abnormalities with key cytokine loops sustaining chronic inflammation, angiogenesis, neuroinflammation, and immune tolerance. Within this circuitry, macrophage polarization, dendritic cell immaturity, NK-cell anergy, Treg expansion, Th17 amplification, and B-cell–mediated autoimmunity converge to establish a microenvironment that enables ectopic endometrial tissues to persist and evade immune clearance. Central cytokine nodes including IL-6, TNF-α, IL-1β, IL-8, IL-17, IL-10, and TGF-β coordinate inflammatory amplification and fibrotic remodeling, forming biochemical hubs that regulate lesion survival and progression. A key novelty of this review is the identification of actionable immunological nodes within this circuitry, providing mechanistic justification for next-generation therapeutic strategies. These include IL-6/STAT3 and IL-17/IL-23 axis inhibitors, NK-cell checkpoint modulation, BAFF-targeted B-cell therapies, Treg/Th17 rebalancing, macrophage reprogramming, and emerging microbiome-based immune correction approaches. The review further outlines a precision immunotherapy paradigm that integrates immune phenotyping, multiplex cytokine profiling, and multi-omics classification to guide individualized treatment selection. By reframing endometriosis through an integrated immunological and translational lens, this review highlights the limitations of conventional hormonal and surgical interventions and underscores the potential of targeted immunomodulation to achieve durable remission, improve fertility outcomes, and reduce recurrence. The proposed framework provides a foundation for future research and clinical trials aimed at developing mechanism-based, patient-specific therapies for genital endometriosis.

Keywords: Cytokine circuitry, Genital endometriosis, Immune dysregulation, Immunotherapy, Macrophage polarization, Microbiome–immune crosstalk, NK-cell dysfunction, Treg–Th17 imbalance

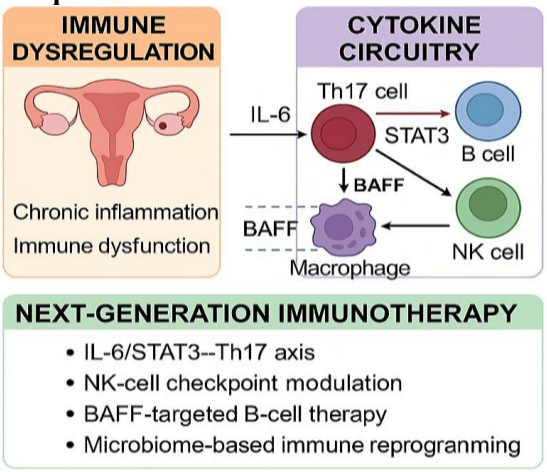
***Author for Correspondence**
Shubham Singh
E-mail: Singhrbgj@gmail.com

[1]B. Pharm Student, Department of Pharmacy, School of Pharmacy, Rai University, Ahmedabad, Gujarat, India
[2]Assistant Professor, Department of Pharmaceutics, School of Pharmacy, Rai University, Ahmedabad, Gujarat, India
[3]Professor and Principal, Department of Pharmaceutics, School of Pharmacy, Rai University, Ahmedabad, Gujarat, India

Received Date: November 05, 2025
Accepted Date: November 13, 2025
Published Date: November 25, 2025

Citation: Yadav Laxmi, Shubham Singh, Sanjesh Rathi. Immune Dysregulation and Cytokine Circuitry in Genital Endometriosis: Mechanistic Insights and Next-Generation Immunotherapeutic Strategies. Research & Reviews: A Journal of Pharmacology. 2026; 16(1): 6–16p.

Graphical Abstract



INTRODUCTION

Genital endometriosis is a chronic, estrogen-dependent inflammatory disorder characterized by the implantation and growth of endometrial-like tissue outside the uterine cavity. Affecting nearly 10% of reproductive-age women, it manifests clinically through pelvic pain, dysmenorrhea, dyspareunia, and infertility, contributing substantially to physical, psychological, and socioeconomic burden [1]. Traditionally viewed as a hormonally driven disease, endometriosis is now recognized as a complex immune-mediated condition in which aberrant inflammatory and immunological pathways play central pathogenic roles. Ectopic lesions display remarkable abilities to evade immune clearance, promote angiogenesis, and remodel surrounding tissue features that cannot be fully explained by retrograde menstruation or hormonal influences alone. Growing evidence reveals that immune dysregulation particularly involving innate and adaptive immune cells such as macrophages, dendritic cells, natural killer (NK) cells, B cells, and T-cell subsets forms the core of the disease's inflammatory microenvironment. Dysfunctional macrophage polarization, impaired NK cytotoxicity, excessive Treg activity, Th17-driven inflammation, and autoantibody production collectively shape an immune milieu that enables lesion establishment, survival, and progression. The cytokine landscape, dominated by IL-1β, IL-6, IL-8, TNF-α, IL-17, and TGF-β, further fuels processes such as angiogenesis, neuroinflammation, fibrosis, and immune evasion. Despite this growing immunological understanding, current management largely relies on hormonal suppression or surgical removal, both of which suffer from recurrence, adverse effects, and limited impact on underlying immune dysfunction. The novelty of this review lies in integrating these fragmented immunological findings into a unified mechanistic framework conceptualized as "cytokine circuitry" that maps the reciprocal interactions between immune cells, cytokine hubs, and lesion microenvironments. This synthesis highlights critical immune-cytokine nodes that can serve as next-generation therapeutic targets beyond conventional hormonal therapies. It also underscores emerging immunotherapies, microbiome-modulating strategies, and immune-phenotype–guided personalized medicine as promising avenues for more durable and precise disease management. By reframing genital endometriosis through an advanced immunological lens, this review provides an updated and translational perspective to guide future therapeutic innovations and research directions [2–4].

SCOPE AND NOVEL CONTRIBUTIONS OF THIS REVIEW

Although substantial progress has been made in understanding endometriosis, current literature remains fragmented, with most studies examining individual immune cells, isolated cytokines, or selective inflammatory pathways. This reductionist approach has limited the development of mechanistically driven therapeutic interventions. To address this gap, the present review synthesizes the immunopathogenesis of genital endometriosis through an integrated, systems-immunology framework, emphasizing the dynamic interplay between innate immunity, adaptive immunity, and cytokine-regulated inflammatory circuits. The scope of this review extends beyond descriptive immunology to highlight translational opportunities for targeted immunomodulation.

The Novel Contributions of this Review are Fivefold

- *Conceptualizing a Unified "Immune–Cytokine Circuitry Model,":* which integrates macrophage polarization, dendritic cell immaturity, NK-cell anergy, Treg/Th17 disequilibrium, and B-cell–mediated autoimmunity into a cohesive pathogenic architecture. This framework identifies cytokine hubs—particularly IL-6, TNF-α, IL-17, IL-10, and TGF-β—as central regulators orchestrating lesion survival, angiogenesis, neuroinflammation, and immune escape.
- *Providing an Advanced Mechanistic Synthesis:* that explains how discrete immune abnormalities converge to form a self-perpetuating inflammatory microenvironment. By merging innate and adaptive immune dysfunctions, this review proposes a more holistic pathophysiological understanding than currently available in the literature.
- *Identifying "Actionable Immunological Nodes":* within cytokine circuits and immune-cell interaction networks that represent high-value targets for next-generation therapeutics, including cytokine-axis blockade, immune-checkpoint modulation, and B-cell–directed interventions.

- *Elucidating the Emerging role of Immune–Microbiome Crosstalk:* in shaping cytokine gradients, estrogen metabolism, mucosal immunity, and systemic inflammatory tone—an area rarely synthesized in prior reviews but increasingly relevant for disease modulation.
- *Proposing a Precision-Immunology Framework:* that incorporates immune phenotyping, multiplex cytokine profiling, and multi-omics signatures to stratify patients and guide personalized immunotherapeutic strategies. This approach offers a forward-looking roadmap for individualized treatment beyond conventional hormonal suppression.

INTEGRATED IMMUNE–CYTOKINE CIRCUITRY IN GENITAL ENDOMETRIOSIS

Genital endometriosis is sustained by a deeply interconnected network of immune cells and cytokine-driven signaling pathways that collectively establish a chronic inflammatory, angiogenic, and immunotolerant microenvironment. Rather than functioning as isolated contributors, innate and adaptive immune components engage in continuous bidirectional communication, forming a complex immune–cytokine circuitry that orchestrates lesion establishment, progression, and immune escape. This integrated model provides a more comprehensive explanation for the persistence and recurrence of endometriosis than traditional hormonal or retrograde menstruation theories alone. At the core of this circuitry is a reciprocal feedback system in which aberrant immune cells drive the production of inflammatory cytokines, while cytokine gradients in turn reprogram immune-cell phenotypes. Key cytokine hubs—including IL-6, TNF-α, IL-1β, IL-8, IL-17, IL-10, and TGF-β—act as central regulators that synchronize macrophage activation, dendritic cell maturation, NK-cell cytotoxicity, T-cell differentiation, and B-cell activation. These cytokines shape the structural and functional landscape of ectopic lesions by promoting neoangiogenesis, neurogenesis, extracellular matrix remodeling, and fibrogenesis [5].

This section synthesizes the current mechanistic knowledge by examining three major components of the integrated circuitry.

- Innate immune drivers, including macrophages, dendritic cells (DCs), and natural killer (NK) cells, which initiate and sustain inflammatory activation while failing to eliminate ectopic endometrial fragments
- Adaptive immune reprogramming, particularly involving Treg/Th17 imbalance and B-cell–mediated autoimmunity, which reinforces immune tolerance and tissue invasion; and
- Cytokine hubs, which serve as the biochemical backbone of lesion survival through coordinated inflammatory signaling.

Innate Immune Drivers Within Cytokine Circuitry

Macrophage Polarization and Pro-Inflammatory Amplification

Macrophages are numerically enriched within the peritoneal fluid and ectopic lesions, yet they exhibit markedly impaired phagocytic activity, permitting the survival of displaced endometrial cells. Driven by cytokines such as IL-6, TNF-α, and IL-1β, these macrophages adopt a predominantly M1-like phenotype characterized by heightened production of pro-inflammatory mediators and matrix metalloproteinases. Through secretion of VEGF, TGF-β, and nerve growth factors, they facilitate neovascularization, fibrotic remodeling, and neuroinflammation—processes that underlie pain and lesion persistence. The reciprocal activation of macrophages by lesion-derived cytokines establishes a self-perpetuating inflammatory loop central to the chronicity of endometriosis [6].

Dendritic Cell Immaturity and Tolerogenic Signaling

DCs in endometriosis exhibit impaired maturation, marked by increased CD1a expression and reduced levels of co-stimulatory molecules such as CD83, CD80, and CD86. This immature phenotype results in inadequate antigen presentation and suboptimal activation of effector T cells, thereby facilitating immune tolerance of ectopic tissue. Cytokines such as IL-10, TGF-β, and prostaglandin E2 within the peritoneal microenvironment further promote DC tolerogenicity and diminish migratory capacity. In parallel, DCs secrete pro-angiogenic factors and promote Treg expansion, reinforcing a microenvironment that favors lesion survival while suppressing effective immune surveillance.

NK-Cell Anergy and Impaired Cytotoxic Surveillance

NK cells, which normally eliminate aberrant or misplaced cells, exhibit diminished cytotoxic activity in women with endometriosis. Elevated levels of IL-6, IL-10, and TGF-β downregulate activating receptors such as NKG2D and suppress production of cytolytic molecules including perforin and granzyme B. Concurrent upregulation of inhibitory receptors (e.g., KIR2DL1, NKG2A) and expression of non-classical MHC class I molecules (HLA-G, HLA-E) on ectopic cells further attenuate NK-cell function. This dual suppression—via soluble cytokines and receptor–ligand interactions—creates a permissive niche wherein ectopic endometrial fragments evade cytotoxic elimination [7].

Integrated Innate Immune Disruption

Together, macrophages, DCs, and NK cells form a dysregulated innate immune triad that drives the early stages of lesion implantation and progression. Their interactions generate sustained cytokine signaling loops, inhibit cytotoxic immunity, promote angiogenesis, and establish immune tolerance. This integrated dysfunction positions innate immunity as a foundational element of the immune–cytokine circuitry and a critical target for next-generation immunotherapies aiming to restore immune clearance and interrupt lesion-supportive pathways.

This integrated dysfunction positions innate immunity as a foundational element of the immune–cytokine circuitry and a critical target for next-generation immunotherapies aiming to restore immune clearance and interrupt lesion-supportive pathways (Table 1) [8–10].

Table 1. Immune cell dysfunctions and their pathogenic contributions in genital endometriosis.

Immune Cell Type	Dysfunction	Major Cytokines/Markers	Pathogenic Consequences
Macrophages	↑numbers, ↓ phagocytosis, M1-like polarization	TNF-α, IL-6, VEGF, TGF-β, MMPs	Chronic inflammation, angiogenesis, neuroinflammation
Dendritic Cells	Immature/tolerogenic phenotype	↓ CD83, ↑ CD1a, IL-10, TGF-β	Impaired antigen presentation, Treg expansion, immune tolerance
NK Cells	↓ cytotoxicity, ↑ inhibitory receptor signaling	↓ Perforin, ↑ KIR2DL1, NKG2A	Failed clearance of ectopic cells, lesion survival
Tregs	Increased abundance, elevated suppressive function	IL-10, TGF-β	Immunosuppression, angiogenesis, lesion tolerance
Th17 Cells	Increased differentiation and activity	IL-17, IL-23, IL-6	Inflammation, fibrosis, angiogenesis
B Cells	Aberrant activation, autoantibody production	BAFF, ANA, AEAs	Autoimmunity, implantation failure, chronic inflammation

Adaptive Immune Reprogramming and Lesion Tolerance

Treg Expansion and Immunosuppressive Conditioning

Tregs ($CD4^+CD25^+FOXP3^+$) are enriched in the peritoneal fluid, eutopic endometrium, and ectopic lesions of women with endometriosis. Their expansion is driven by high local concentrations of IL-10 and TGF-β, which enhance FOXP3 expression and promote suppressive phenotypes. Elevated Treg activity dampens cytotoxic T-cell responses and suppresses antigen-specific immunity, thereby reducing clearance of ectopic endometrial cells. Beyond immunosuppression, Tregs contribute to lesion progression through VEGF-mediated angiogenic support, reinforcing vascular networks essential for lesion maintenance. The chronic Treg-dominated environment thus forms a key tolerogenic axis that protects ectopic tissue from immune attack [11].

Th17 Amplification and Sustained Inflammation

In contrast to Tregs, Th17 cells ($CD4^+ROR\gamma t^+$) are potent drivers of inflammation and tissue invasion. Elevated levels of IL-6, IL-1β, IL-23, and prostaglandin E2 in the peritoneal cavity facilitate differentiation of naïve T cells toward the Th17 lineage. Th17-derived IL-17 promotes recruitment of neutrophils and macrophages, enhances expression of MMPs, and stimulates angiogenic and fibrogenic

pathways, thereby accelerating lesion invasiveness and chronic pain. Increased Th17 activity correlates with lesion severity and contributes to the self-amplifying inflammatory circuit characteristic of advanced disease.

Disrupted Treg–Th17 Equilibrium as a Pathogenic Switch

The balance between Tregs and Th17 cells is tightly regulated by cytokine context; TGF-β alone promotes Treg differentiation, whereas TGF-β combined with IL-6 drives Th17 polarization. In endometriosis, elevated IL-6 disrupts this equilibrium, shifting immune homeostasis toward a state of concurrent inflammation and immune tolerance. This paradoxical coexistence permits lesions to evade immune destruction while perpetuating chronic inflammatory injury–a central feature of adaptive immune dysfunction in endometriosis.

B-Cell Activation and Autoantibody-Mediated Dysfunction

B cells and humoral immunity further contribute to adaptive reprogramming. Women with endometriosis exhibit increased levels of autoantibodies, including anti-endometrial, anti-nuclear, anti-phospholipid, and anti-ovarian antibodies. These arise from a cytokine-rich environment characterized by elevated BAFF, which supports survival and maturation of autoreactive B cells. Autoantibody production promotes complement activation, immune complex deposition, and chronic inflammation, while interfering with reproductive processes such as implantation and sperm–oocyte interaction. Ectopic lymphoid aggregates resembling tertiary lymphoid structures within lesions enable local antigen presentation and autoantibody refinement, deepening humoral dysregulation.

Integrated Adaptive Immune Reprogramming

The combined effects of Treg expansion, Th17 activation, and B-cell–driven autoimmunity form a powerful adaptive immune network that reinforces lesion tolerance, chronic inflammation, fibrosis, and infertility. These mechanisms interact synergistically with innate immune abnormalities to sustain a self-propagating immune–cytokine circuitry that underpins the chronic, recurrent nature of endometriosis.

Cytokine Hubs Coordinating Lesion Survival

IL-6: A Central Driver of Inflammation and Immune Polarization

IL-6 is one of the most consistently elevated cytokines in the serum, peritoneal fluid, and lesions of women with endometriosis. Its pleiotropic effects extend across both innate and adaptive immunity. IL-6 synergizes with TGF-β to promote Th17 differentiation, amplifying IL-17–mediated tissue invasion and neutrophil recruitment. Simultaneously, IL-6 inhibits Treg development, disrupting immune tolerance equilibrium. In innate cells, IL-6 suppresses NK-cell cytotoxic molecules (granzyme B and perforin) and shifts macrophages toward an inflammatory phenotype. Through these mechanisms, IL-6 represents a major "command node" linking inflammatory amplification, immune suppression, and lesion survival [12].

TNF-α: Orchestrator of Tissue Remodeling and Angiogenesis

TNF-α, primarily produced by activated macrophages and ectopic stromal cells, plays a pivotal role in driving extracellular matrix degradation and fibrosis. By activating MMPs and promoting VEGF expression, TNF-α contributes to angiogenesis, tissue remodeling, and lesion progression. It also enhances recruitment of monocytes and neutrophils, intensifying local inflammation. Although TNF-α has been explored as a therapeutic target, mixed clinical trial results highlight the complexity of its interactions within the broader cytokine network.

IL-1β and IL-8: Acute Inflammatory Mediators

IL-1β acts as an upstream activator of multiple inflammatory pathways, enhancing prostaglandin synthesis, cellular adhesion, and angiogenesis. It also drives IL-6 and IL-8 production, creating an early inflammatory cascade that promotes lesion implantation. IL-8, in turn, is a potent chemokine that recruits neutrophils and stimulates angiogenesis. Elevated IL-8 levels correlate strongly with lesion

invasiveness and pelvic pain, underscoring its role in cellular infiltration and neuroinflammatory signaling.

IL-17: A Potent Effector of Fibrosis and Invasion

Produced predominantly by Th17 cells, IL-17 promotes stromal cell proliferation, MMP expression, and fibroblast activation. It also synergizes with IL-6, IL-1β, and TNF-α to amplify inflammation. IL-17–driven neutrophil recruitment and extracellular matrix remodeling contribute to progressive fibrosis and chronic pelvic pain. Elevated IL-17 levels correlate with disease severity, making it an attractive target for immunomodulatory therapy.

IL-10 and TGF-β: Pillars of Immune Tolerance and Fibrogenesis

Though traditionally considered anti-inflammatory, IL-10 and TGF-β play paradoxical roles in endometriosis by promoting immune tolerance and facilitating lesion survival. IL-10 inhibits antigen presentation and cytotoxic T-cell activity, protecting ectopic cells from immune-mediated destruction. TGF-β contributes to fibrogenesis, angiogenesis, and epithelial–mesenchymal transition (EMT), supporting lesion expansion. Together, these cytokines create a permissive microenvironment that allows persistent inflammation while simultaneously suppressing effective immune clearance [13].

Integrated Cytokine Hub Dynamics

The interaction of these cytokines forms a tightly coordinated signaling web in which pro-inflammatory and immunosuppressive pathways coexist. This dual signaling enables lesions to invade surrounding tissue while avoiding immune elimination. The integration of IL-6, TNF-α, IL-17, IL-10, and TGF-β into a unified cytokine circuitry model provides a mechanistic framework for understanding endometriosis as a chronic, self-sustaining immunological disorder. This cytokine-centric perspective identifies multiple high-value therapeutic targets and offers a foundation for rational design of next-generation immunotherapies [14].

LIMITATIONS OF CURRENT HORMONAL AND SURGICAL TREATMENTS

Limitations of Hormonal Therapy

Hormonal treatments–including combined oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists and antagonists, and aromatase inhibitors–aim to suppress estrogen production and reduce the proliferative activity of ectopic tissue. However, several inherent limitations constrain their long-term effectiveness.

- *Non-Curative and Palliative Nature:* Hormonal agents suppress but do not eradicate lesions. Symptoms frequently recur after treatment cessation, reflecting persistent immune dysregulation and cytokine-driven inflammation.
- *Limited Benefit for Fertility:* Ovulation suppression impairs natural conception, and clinical evidence consistently demonstrates minimal improvement in fertility outcomes despite hormonal control of pain.
- *Systemic Adverse Effects:* Long-term hypoestrogenism from GnRH analogues leads to vasomotor symptoms, bone mineral density loss, sexual dysfunction, and mood alterations, necessitating add-back therapy.
- *Incomplete Control of Inflammatory Pathways:* Hormonal suppression does not adequately modulate key cytokines—such as IL-6, TNF-α, IL-1β, and IL-17—nor does it correct macrophage, NK-cell, or T-cell imbalances, limiting therapeutic durability.

Limitations of Surgical Management

Laparoscopic excision or ablation remains a cornerstone for diagnosis and treatment, especially in moderate-to-severe disease or refractory pain. Despite its clinical utility, surgery faces several critical challenges.

- *High Recurrence Rates:* Recurrence of pain or lesions occurs in up to 50% of patients within five years, largely due to the persistence of microscopic implants and unaddressed immunological

dysfunction.

- *Risks Associated with Invasive Procedures:* Surgical complications such as bleeding, infection, organ injury, and adhesions contribute to morbidity, particularly in cases of deep infiltrating endometriosis.
- *Impact on Reproductive Outcomes:* Although surgical removal of moderate-to-severe disease may improve fertility, repeated ovarian surgeries reduce ovarian reserve, compromising long-term reproductive potential.
- *Operator Dependence and Access Limitations:* Surgical expertise varies significantly across centers, leading to inconsistent outcomes. Access to advanced laparoscopic or specialized endometriosis centers remains limited globally.
- *Failure to Address Immunopathogenesis:* Surgery removes macroscopic lesions but does not eliminate circulating inflammatory mediators, immune imbalances, or cytokine hubs. Persistent elevation of IL-6, IL-8, TNF-α, and TGF-β continues to promote lesion regeneration and pain [15].

Clinical Gaps

Both hormonal and surgical treatments address the downstream manifestations of endometriosis rather than its upstream immunological drivers. The inability of these therapies to modulate macrophage dysfunction, NK-cell anergy, Treg–Th17 imbalance, cytokine circuitry, and microbiome dysbiosis explains the high recurrence rates and variable clinical responses. These limitations underscore the urgent need for therapies that target the biological mechanisms sustaining chronic inflammation and immune tolerance [16].

TRANSLATIONAL IMMUNOLOGY: ACTIONABLE THERAPEUTIC NODES

Recent advances in immunopathogenesis have highlighted multiple "actionable nodes" within the immune–cytokine circuitry of genital endometriosis. These nodes represent mechanistic leverage points where immunological dysfunction converges to sustain chronic inflammation, fibrosis, and immune tolerance. Targeting these nodes has the potential to disrupt the pathogenic feedback loops that reinforce lesion survival, making them promising candidates for next-generation therapeutic development. This translational perspective bridges mechanistic insights with clinical applicability and offers a novel framework for precision immunomodulation [17].

IL-6/STAT3–Driven Th17 Polarization

The IL-6/STAT3 axis is a central driver of Th17 differentiation and a major contributor to the inflammatory phenotype of endometriosis. Persistent activation of this pathway fosters IL-17 production, neutrophil recruitment, and stromal invasion. Inhibiting this node–through IL-6 receptor antagonists, STAT3 inhibitors, or IL-17 blockade–directly targets the pro-inflammatory arm of adaptive immunity. This approach is supported by preclinical data demonstrating restoration of NK-cell cytotoxicity and reduction in Th17-associated cytokines following IL-6 inhibition.

NK-Cell Checkpoint Modulation

NK-cell dysfunction arises from excessive signaling through inhibitory receptors (e.g., KIR2DL1, NKG2A) and reduced activating receptor engagement (e.g., NKG2D). Therapeutically blocking these inhibitory checkpoints or restoring activating receptor expression could reinstate cytotoxic clearance of ectopic cells. Insights from cancer immunotherapy, where NK-cell checkpoint inhibitors and adoptive NK-cell therapies have shown efficacy, provide a strong translational foundation for applying similar strategies to endometriosis.

BAFF–B Cell Axis and Autoantibody Suppression

B-cell hyperactivation and autoantibody production are supported by elevated BAFF levels in serum and peritoneal fluid. BAFF-driven survival of autoreactive clones contributes to chronic inflammation, complement activation, and infertility. Targeting this node using BAFF inhibitors (e.g., belimumab) or

anti-CD20 therapies (e.g., rituximab) may modulate humoral autoimmunity and reduce autoantibody-mediated tissue injury. This therapeutic direction is particularly relevant for patients exhibiting strong autoimmune signatures.

Treg Stabilization and Correction of Immune Tolerance

The expansion and hyperactivity of Tregs–driven by IL-10, TGF-β, and estrogen–protect ectopic lesions from immune clearance. Strategies aimed at modulating Treg plasticity, such as low-dose IL-2 therapy, retinoic acid, or vitamin D analogues, may help restore balanced immune tolerance without inducing excess suppression. Targeted adjustment of the Treg/Th17 axis represents a promising precision approach for selective immune recalibration.

Macrophage Reprogramming and Resolution of Inflammation

Macrophages in endometriosis are skewed toward a pro-inflammatory, lesion-promoting phenotype. Modulating their polarization through CSF-1R inhibitors, TLR antagonists, or reprogramming agents (e.g., PPAR-γ agonists) may disrupt cytokine-driven inflammation, angiogenesis, and fibrosis. Reversing macrophage dysfunction could restore phagocytic clearance of ectopic cells and diminish lesion-supportive microenvironments.

Microbiome-Targeted Immunomodulation

Microbiome dysbiosis influences immune activation and cytokine gradients through LPS-mediated TLR signaling, SCFA depletion, and estrogen recycling. Probiotic strategies, prebiotic supplementation, short-chain fatty acid enhancers, and fecal microbiota transplantation (FMT) represent emerging interventions aimed at restoring mucosal immunity and reducing cytokine-mediated inflammation. Microbiome correction is increasingly recognized as an upstream therapeutic node capable of modifying both immune and hormonal pathways.

Multi-Node Combination Approaches

Given the interconnected nature of immune–cytokine circuits, targeting individual nodes may not produce durable remission. Combination approaches–such as IL-6 inhibition with NK-cell activation or BAFF blockade combined with macrophage reprogramming–offer potential synergistic effects by simultaneously addressing inflammatory and immunosuppressive arms of the circuitry. Early mechanistic studies support the concept that multi-node modulation may be more effective than single-pathway interventions.

Toward Precision Immunotherapy

Actionable nodes identified within this circuitry support a precision medicine paradigm that classifies patients based on cytokine profiles, immune-cell phenotypes, microbial signatures, and molecular clusters. Stratifying patients according to immune-dominant pathways (e.g., IL-6-high, BAFF-high, Th17-predominant, NK-cell–suppressed) may optimize therapeutic responsiveness and reduce treatment resistance [18–20].

EMERGING THERAPEUTIC STRATEGIES

The deepened understanding of immune–cytokine circuitry in genital endometriosis has catalyzed the development of innovative therapeutic avenues aimed at correcting underlying immunological dysregulation rather than merely suppressing hormonal activity. These emerging strategies target specific immunopathogenic nodes–including cytokine hubs, NK-cell inhibitory pathways, B-cell activation, microbiome-driven inflammation, and Treg/Th17 imbalance–and represent a paradigm shift toward mechanism-based, durable treatments. The following subsections highlight the most promising next-generation immunotherapeutic and microbiome-modulating approaches.

Cytokine-Targeted Immunotherapies

Cytokine-blocking biologics have gained prominence due to their ability to disrupt central inflammatory pathways.

- *IL-6/IL-6R Inhibitors (e.g., Tocilizumab, Sarilumab):* By blocking IL-6 signaling, these agents reduce Th17 differentiation, restore NK-cell cytotoxicity, and suppress macrophage-driven inflammation. Preclinical studies demonstrate decreased lesion growth and normalization of inflammatory cytokines after IL-6 blockade.
- *IL-17/IL-23 Axis Inhibitors (e.g., Secukinumab, Ustekinumab):* Given IL-17's role in fibrosis and stromal invasion, IL-17 inhibitors may attenuate lesion invasiveness and chronic pelvic pain. IL-23 inhibition reduces Th17 expansion, offering upstream pathway control.
- *TNF-α Inhibitors (e.g., Infliximab, Adalimumab):* Although clinical outcomes have been mixed, TNF-α blockade remains relevant for subsets of patients with hyperinflammatory phenotypes or deep infiltrating lesions. The mixed results likely reflect heterogeneous cytokine profiles, highlighting the need for immune phenotyping.
- *TGF-β Modulators:* Experimental therapies that modulate TGF-β signaling show promise in reducing fibrosis and epithelial–mesenchymal transition (EMT), addressing structural components of lesion persistence.

NK-Cell Checkpoint Modulation

NK-cell dysfunction in endometriosis mirrors mechanisms observed in tumor immune evasion. Therapeutic approaches include.

- Anti-NKG2A or anti-KIR antibodies to block inhibitory signaling.
- Agents that upregulate NKG2D expression on NK cells.
- Adoptive transfer of activated or engineered NK cells, offering an ex vivo method to bypass local immunosuppression.

BAFF–B Cell Axis Modulation

BAFF is a critical survival factor for autoreactive B cells. Targeting this axis provides a novel approach for patients with pronounced autoimmune signatures:

- Belimumab (anti-BAFF) reduces B-cell overactivation and autoantibody production.
- Rituximab (anti-CD20) induces B-cell depletion and is particularly beneficial in refractory autoimmune-mediated infertility.

Microbiome-Based Immune Reprogramming

Microbiome interventions represent an upstream strategy capable of modifying immune, hormonal, and epithelial homeostasis.

- *Probiotics (Lactobacillus-Dominant Formulations):* Restore reproductive tract eubiosis, reduce IL-8 and TNF-α levels, and improve mucosal barrier integrity.
- *Prebiotics and Synbiotics:* Support SCFA-producing bacteria and modulate Treg/Th17 balance via butyrate-mediated immunoregulation.
- *Short-Chain Fatty Acid (SCFA) Supplementation:* Butyrate and propionate supplementation decreases macrophage activation and reduces cytokine gradients driving lesion survival.
- *Fecal Microbiota Transplantation (FMT):* An emerging experimental therapy, FMT re-establishes immune-regulating microbial communities and normalizes the estrobolome.

Precision Immunotherapy Using Immune Phenotyping

Given the heterogeneity of immunological signatures among patients, stratified treatment offers greater therapeutic efficiency.

- *IL-6–High Phenotypes:* respond better to IL-6/IL-6R inhibitors.
- *Th17-Predominant Phenotypes:* benefit from IL-17/IL-23 blockade.
- *NK-Cell–Suppressed Profiles:* may require checkpoint inhibition or NK-cell infusion.
- *BAFF-Dominant Phenotypes:* suitable for B-cell–targeted therapies.

Combination and Hybrid Immunomodulatory Approaches

Given the complexity and redundancy of immune–cytokine circuits, monotherapies may only partially reduce inflammation. Combination strategies–such as IL-6 inhibition plus NK-cell activation,

or BAFF blockade paired with microbiome correction–offer synergistic potential. Early models suggest multi-target immunomodulation significantly reduces cytokine overflow, immune tolerance, and lesion recurrence compared to single-agent therapy [21].

Non-Pharmacological Adjuncts for Immune Regulation

Lifestyle interventions that complement immunotherapy include:

- Anti-inflammatory diets rich in omega-3 fatty acids, antioxidants, and polyphenols
- Physical therapy-based approaches that modulate neuroimmune pain pathways
- Stress reduction and cognitive-behavioral therapy, which lower cortisol-driven immune activation [22–25].

CONCLUSIONS

Genital endometriosis is no longer understood solely as an estrogen-dependent disorder but as a complex, immune-mediated disease driven by tightly interconnected networks of dysregulated immune cells, cytokine hubs, and microbiome-derived modulators. The integrated immune–cytokine circuitry model presented in this review highlights how macrophage polarization, dendritic cell immaturity, NK-cell anergy, Treg/Th17 imbalance, and B-cell–mediated autoimmunity collectively generate a chronic inflammatory, angiogenic, and immunotolerant microenvironment that sustains ectopic lesion survival. These mechanisms explain the limitations of conventional hormonal and surgical therapies, which do not address the upstream immunological drivers of recurrence, persistent pain, and impaired fertility. By synthesizing contemporary mechanistic insights, this review identifies multiple actionable immunological nodes–including the IL-6/STAT3–Th17 axis, NK-cell checkpoints, BAFF-mediated B-cell activation, Treg plasticity, and macrophage polarization–that offer promising targets for next-generation immunotherapies. Emerging microbiome-based interventions further expand the therapeutic landscape by modulating estrogen recycling, mucosal immunity, and systemic cytokine balance. Together, these findings support a paradigm shift toward precision immunomodulation and patient-specific therapeutic stratification based on immune phenotyping, cytokine profiling, and multi-omics signatures. Moving forward, successful management of endometriosis will require integrating immunological correction with hormonal, surgical, and supportive strategies to achieve durable remission, restore reproductive function, and improve quality of life. The translational framework outlined in this review provides a foundation for future therapeutic innovation and underscores the urgent need for clinical trials evaluating targeted immunotherapies in well-defined immunological endotypes. Through this integrated lens, advancing endometriosis care becomes not only possible but achievable through scientifically grounded, immune-informed precision medicine.

REFERENCES

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789–1799.
2. Bulun SE. Endometriosis. N Engl J Med. 2009;360(3):268–279.
3. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertil Steril. 2001;75(1):1–10.
4. Wu MY, Ho HN. The role of cytokines in endometriosis. Am J Reprod Immunol. 2003;50(6):389–396.
5. May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations and biomarkers in endometriosis. Hum Reprod Update. 2011;17(6):637–653.
6. Dmowski WP, Braun DP. Immunology of endometriosis. Am J Reprod Immunol. 1995;33(2):120–129.
7. Bedaiwy MA, Falcone T. Peritoneal fluid cytokines in endometriosis. Reprod Biomed Online. 2007;15(3):266–275.
8. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Gynecol Obstet Invest. 1997;43(1):48–56.
9. Kyama CM, et al. Cytokine expression in endometriosis. Reprod Biol Endocrinol. 2003;1:123.
10. Herington JL, Brasted M, et al. Immune interactions in endometriosis. Hum Reprod Update.

2011;17(4):415–426.
11. Ulukus M, Arici A. Immunology of endometriosis. Curr Opin Obstet Gynecol. 2005;17(4):375–382.
12. Viganò P, Somigliana E, Vercellini P, et al. Cytokines and growth factors in endometriosis. Hum Reprod Update. 2003;9(5):453–467.
13. Tariverdian N, et al. Immunological profile of endometriosis. J Reprod Immunol. 2009;83(1-2):39–43.
14. Ahn SH, Monsanto SP, Miller C, et al. Pathophysiology of endometriosis. Biol Reprod. 2015;92(2):123–135.
15. Aredo JV, et al. Immune dysregulation in women with endometriosis. Obstet Gynecol Clin North Am. 2021;48(2):247–266.
16. Sun PR, Leng JH, Yu JH, et al. NK cell cytotoxicity in endometriosis. Fertil Steril. 2006;86(6):1532–1537.
17. Ho HN, Wu MY, et al. Macrophages in peritoneal endometriosis. Am J Reprod Immunol. 1997;38(6):400–412.
18. Capobianco A, Monno A, et al. Tie2+ macrophages in endometriosis. Am J Pathol. 2011;179(5):2651–2659.
19. Ahn SH, Singh V, Tayade C. Cytokine–immune interactions. Am J Reprod Immunol. 2017;78(3):e12618.
20. Králíčková M, et al. Immunopathogenesis of endometriosis. Ann N Y Acad Sci. 2018;1411(1):5–22.
21. Khan KN, Kitajima M, et al. Role of bacterial contamination in endometriosis. Reprod Med Biol. 2018;17(2):125–133.
22. Wang XQ, et al. IL-17 in endometriosis. Reprod Sci. 2018;25(7):1044–1053.
23. Borrelli GM, et al. Macrophage dynamics in endometriosis. Front Immunol. 2021;12:671103.
24. Suryawanshi S, et al. Treg and Th17 imbalance in endometriosis. Am J Reprod Immunol. 2015;73(2):174–182.
25. Ata B, Yildiz S, Turkgeldi E, et al. Endometriosis and microbiome: a systematic review. Reprod Sci. 2020;27(3):844–856.

