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Review

The Role of Immune Cells and Cytokines in the Pathogenesis and Treatment of Genital Endometriosis

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Abstract: Genital endometriosis is a chronic inflammatory condition characterized by immune dysfunction involving both innate and adaptive immunity. Disrupted immune responses, particularly those involving macrophages, dendritic cells, natural killer cells, regulatory T cells, T helper 17 cells, and B-cell-driven autoimmunity, create an environment conducive to ectopic endometrial tissue survival. The cytokine milieu, marked by elevated levels of interleukin-6, tumor necrosis factor-alpha, and interleukin-10, facilitates the interaction between inflammation and immune tolerance, thereby driving disease progression. Current hormonal and surgical treatments offer only temporary or partial symptom relief and fail to address the underlying immunopathogenic mechanisms of the disease. Their limitations, including high recurrence rates, systemic side effects, and insufficient fertility restoration, highlight the need for novel interventions that target specific pathways. Recent advances in immunology and microbiome research have led to promising therapeutic strategies, such as microbiome modulation, precision medicine based on immune phenotyping, and integrative care models that provide personalized and comprehensive treatment. Future research should focus on advancing immune and microbial profiling to guide targeted therapies, validating immunomodulatory approaches, and integrating these methods into clinical practices. By bridging basic research with clinical applications, the field is poised to shift from managing symptoms to altering the disease trajectory, ultimately improving outcomes for women affected by genital endometriosis.

Keywords: Genital Endometriosis; Immune Dysfunction; Macrophages; Natural Killer Cells; Dendritic Cells

1. Introduction

Genital endometriosis is characterized by endometrial-like glands and stroma outside the uterine cavity, but restricted to the genital tract. It affects organs such as the ovaries, fallopian tubes, uterosacral ligaments, pelvic peritoneum, cervix, and vagina [1–3]. Ectopic endometrial tissue remains responsive to hormones, leading to inflammation, fibrosis, and adhesions due to menstrual hormonal fluctuations [3].

Genital endometriosis contributes to chronic pelvic pain syndrome in women of reproductive age, affecting 10–15% of this population [3, 4]. Pain manifests as severe dysmenorrhea, non-cyclic pelvic pain, painful intercourse, and difficulty in bowel movements. This discomfort is related to local inflammatory responses in implants and neural mechanisms, with increased neurogenesis in lesions [3]. Symptoms intensify during menstruation due to cyclic bleeding in ectopic tissue, and persistent pain can disrupt daily activities and diminish the quality of life [2,4,5].

Endometriosis contributes to infertility and is identified in 25–50% of women undergoing infertility evaluations, compared to 0.5–5% in fertile women [1,4,6]. The reasons are complex: adhesions and fibrosis alter the pelvic structure, impeding gamete movement. Increased peritoneal macrophage numbers and higher levels of cytokines and growth factors disrupt reproductive functions, such as ovulation, fertilization, and embryo development [7,8]. The peritoneal fluid contains proinflammatory substances that interfere with fallopian tube and endometrial function, hindering implantation [7]. Endometriomas may reduce the ovarian reserve and oocyte quality [6]. The fecundity rate in women with endometriosis is approximately half that of women with tubal infertility [7].

While most women with endometriosis have regular cycles, many report menorrhagia, metrorrhagia, or shortened cycles, which are risk factors for outflow obstruction or hormonal alterations [4], leading to infertility. Chronic pelvic pain and infertility-related stress create psychosocial burdens, with higher rates of depression, anxiety, social withdrawal, and work absenteeism [2,5].

Endometriosis progresses and recurs with time. Diagnosis takes 7–10 years and requires multiple doctor visits, imaging tests, and surgeries, such as laparoscopies and implant removal [2,4]. These procedures and continuous medical treatments impose financial strain on individuals and the healthcare system. Women with endometriosis face a higher risk of certain ovarian cancers, particularly clear cell and endometrioid carcinomas, and rarely, endometriotic lesions may become malignant [2].

Studies have suggested interactions between the genital and gut microbiomes and the development of endometriosis. Microbiome imbalance can increase inflammation and pain, affecting fertility and offering new diagnostic and therapeutic strategies [5,8,9].

The treatment of endometriosis primarily involves hormonal suppression and surgical removal, which offer limited relief and are associated with recurrence and side effects [10,11]. This gap in effectiveness has driven the exploration of alternative therapies that address immune-inflammatory and oxidative stress processes. Modified antioxidant compounds, such as N-acetylcysteine, resveratrol, curcumin, epigallocatechin gallate, and melatonin, have shown promise in reducing oxidative stress, inhibiting nuclear factor-κB/signal transducer and activator of transcription 3 signaling, and influencing angiogenic and neuroinflammatory pathways in preclinical and early clinical research [12–15]. Agents targeting cytokines such as interleukin-6 receptor (IL-6R), IL-17/23 inhibitors, therapies directed at B-cells/B-cell activating factor (BAFF), and microbiome-based approaches are emerging as promising immunological strategies [16–18].

These developments highlight the need to reconceptualize endometriosis as a systemic immune disorder and explore treatments beyond hormone-based therapies. This review consolidates findings on the immunopathogenesis of genital endometriosis, focusing on dysfunctions in innate and adaptive immunity, cytokine networks, oxidative stress, and microbiome changes that drive disease progression. We assessed therapeutic strategies, including biologics targeting cytokines, B-cell/BAFF therapies, natural killer (NK) cell function restoration, antioxidant compounds such as N-acetylcysteine, resveratrol, curcumin, epigallocatechin gallate, and melatonin, and microbiome interventions. This review provides a translational framework for precision medicine approaches to improve clinical outcomes in patients with genital endometriosis.

This review clarifies the immunopathogenic processes in genital endometriosis, emphasizing the roles of innate and adaptive immune cells, such as macrophages, dendritic cells (DCs), NK cells, T helper 17 (Th17) cells, and regulatory T cells (Tregs). It examines the effects of cytokines, autoantibodies, and the microbiome. By integrating immunological and microbiological knowledge, this review identifies new therapeutic targets beyond traditional hormonal and surgical approaches.

2. Methods

This narrative review compiles and contextualizes evidence regarding the immunopathogenesis of genital endometriosis, emphasizing immune cell dysfunction, cytokine regulation, and microbiome interactions. Owing to the complexity of the topic, a structured yet adaptable qualitative synthesis method was used. The aim is to encompass mechanistic research and identify new therapeutic targets beyond traditional hormonal and surgical treatments.

This narrative review employed a systematic and reproducible methodology to identify relevant studies. We searched PubMed/MEDLINE from January 2000 to June 2024 for studies in English, using combinations of terms such as “endometriosis,” “genital endometriosis,” “macrophage,” “dendritic cell,” “natural killer,” “Treg,” “Th17,” “IL-6,” “TNF,” “IL-10,” “microbiome,” “BAFF,” “autoantibody,” and “immunotherapy.” The eligibility criteria included

original research and reviews focused on the immunopathogenesis (innate/adaptive immunity, cytokines) or microbiome interactions in genital endometriosis, while case reports, letters, studies not centered on genital issues, and non-immunologic topics were excluded. Screening was conducted independently by two reviewers who examined the titles and abstracts, followed by the full texts, with any disagreements resolved through consensus.

Although this is a narrative review, we followed systematic guidelines for selecting the literature. To enhance transparency, we included a study selection flowchart (**Figure 1**), adapted from the PRISMA 2020 framework, to summarize the identification, screening, eligibility, and inclusion of the studies.

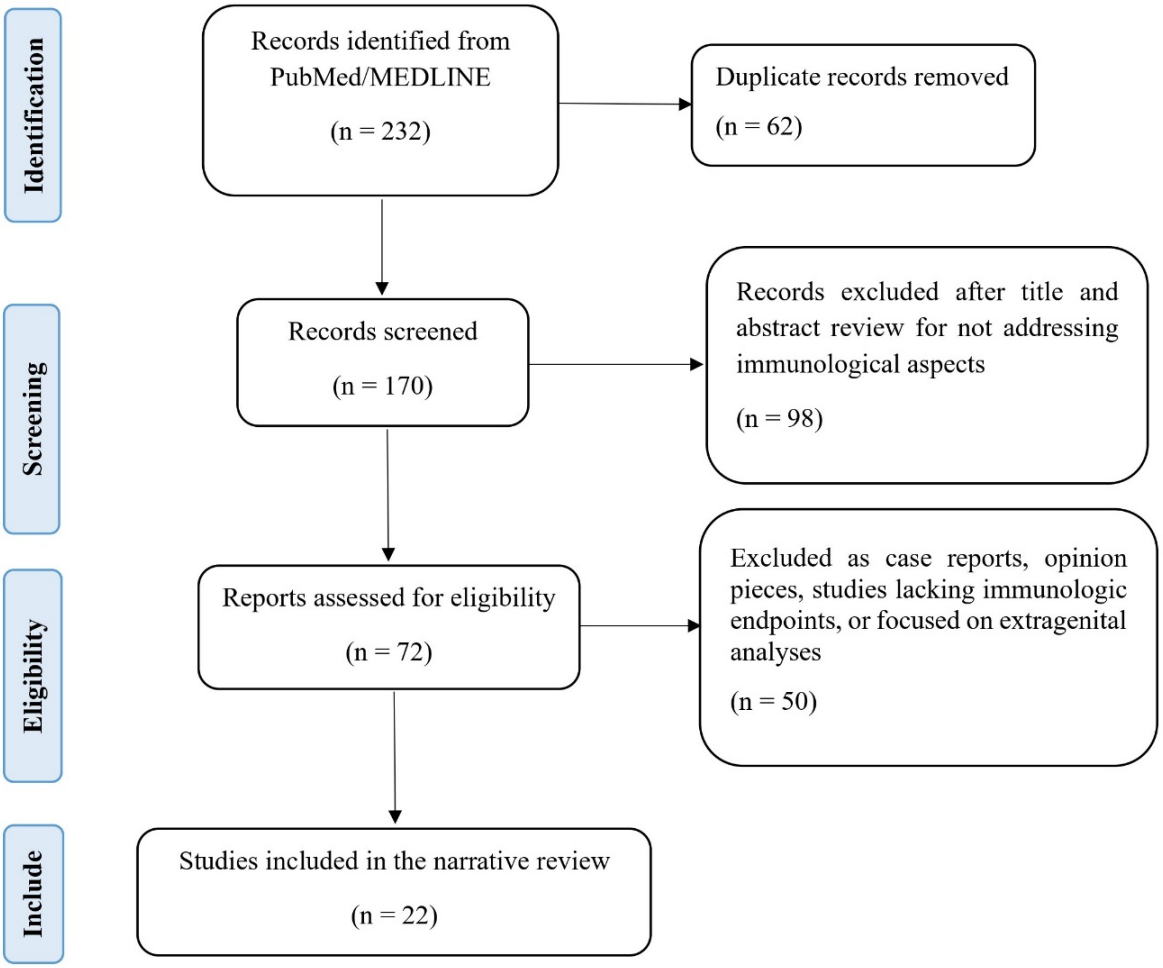

Figure 1. flow diagram of the literature search and study selection for the narrative review.

Eligible studies included original research articles, systematic reviews, and narrative reviews that addressed the immunological and microbiological aspects of genital endometriosis. Studies were selected if they investigated mechanisms involving innate or adaptive immune responses, cytokine signaling, or alterations in the genital or gut microbiota. Human and animal studies and *in vitro* models were considered. The exclusion criteria were case reports, opinion pieces, letters to the editor, and studies focused on extragenital endometriosis without immunological relevance.

After initially screening the titles and abstracts, the full texts of the selected articles were thoroughly examined. Data relevant to the study were extracted and organized thematically, with the findings categorized into key areas: innate immunity (macrophages, DCs, and NK cells), adaptive immunity (Tregs, Th17 cells, and autoantibodies), cytokine networks, and microbiome dynamics. The focus was on studies that provided mechanistic insights, detailed immunophenotyping profiles, and practical implications of immune modulation strategies. Although formal quality assessment tools were not used, studies with robust methodologies and well-defined immunological endpoints

were prioritized.

The integration of themes developed a detailed narrative framework that underscores immune system dysfunction and microbial imbalance in the pathophysiology of endometriosis. This synthesis connects basic immunology with clinical significance, guiding future research and advances in diagnosis and treatment.

3. Results

A PubMed/MEDLINE search between 2000 and 2024 yielded 232 records. After removing duplicates (n = 62), 170 records remained for review. Of these, 98 articles were excluded after title and abstract review for not addressing the immunological or microbiological aspects of genital endometriosis. The remaining 72 articles were subjected to full-text review. After applying the eligibility criteria, 50 articles were excluded as case reports, opinion pieces, studies without immunologic endpoints, or those focused on extragenital analyses. Finally, 22 studies were included in the qualitative narrative synthesis, providing insights into immune dysfunction, cytokine regulation, oxidative stress, and microbiome changes associated with genital endometriosis. The flow chart shows the identification, screening, eligibility, and inclusion processes, adapted from PRISMA 2020, to enhance transparency in the narrative review (**Figure 1**).

4. Limitations of Current Treatments

Despite years of research and new management approaches, current options for treating genital endometriosis, hormonal treatments, and surgical procedures face significant challenges in terms of effectiveness, safety, and patient-centered outcomes.

4.1. Limitations of Hormonal Therapy

Hormonal treatments, including oral contraceptives, progestins, gonadotropin hormone-releasing hormone agonists/antagonists, and aromatase inhibitors, function by reducing systemic or local estrogen levels to render endometriotic implants inactive. These therapies have notable drawbacks:

- Hormonal treatments suppress the activity of endometriotic lesions but do not eliminate them. Symptoms reappear after treatment, indicating their palliative nature [19–21].
- Hormonal therapy does not improve fertility in women with endometriosis and may delay conception by inhibiting ovulation [1,6,21].
- Gonadotropin hormone-releasing hormone analogs cause side effects such as hot flushes, reduced bone density, and sexual dysfunction, requiring add-back therapy. Androgens and aromatase inhibitors have significant off-target effects, which can impact patient compliance and quality of life [19–21].
- Hormonal therapies are unsuitable for women seeking to conceive because of their contraceptive effects [1,6,21].
- Current hormonal regimens do not address the inflammatory, immunological, or neuroangiogenic mechanisms that are crucial for endometriosis progression [3,19]. Many patients experience persistent pain or atypical symptoms, even with maximum hormonal suppression.

4.2. Limitations of Surgery

Surgery through ablation or excision of lesions via laparoscopy remains fundamental for diagnosis and for symptomatic or treatment-resistant cases of endometriosis. The notable limitations of this study are as follows:

- Up to 50% of women experience pain or lesion return within five years [19,22]. Complete excision is often limited by microscopic disease or lesions in surgically challenging areas.
- Surgery involves the risk of bleeding, infection, and potential injury to nearby organs, particularly in advanced or deeply infiltrating diseases [19,22].
- While removing moderate to severe disease may enhance fertility rates, the benefits of minimal disease are less clear, and repeated ovarian surgeries can reduce ovarian reserve, decreasing fertility [1,6,22].
- Surgical outcomes depend on the operator's skill; however, access to skilled laparoscopic surgeons or endometriosis centers remains limited, leading to inconsistent results [19,22].

- Surgery only addresses macroscopic disease; pain and inflammation may persist due to remaining lesions, immunological dysregulation, or central sensitization [3,19].

4.3. Broader and Emerging Limitations

- Endometriosis appears in various forms; however, treatments are uniform, ignoring disease variability or specific mechanisms (e.g., peritoneal, ovarian, or deep infiltrating disease; pain versus infertility) [2,3,19].
- New findings on the microbiome, immune dysfunction, and neuroangiogenesis in endometriosis are not addressed by current treatments, which focus on lesion removal or hormone suppression [3,5,8,19].
- Vague symptoms and late diagnosis result in years of suffering before treatment, when relief or fertility restoration is less likely [2,19].
- Persistent pain, recurring symptoms, and infertility, which are poorly managed by standard treatments, cause significant psychosocial and quality-of-life issues, necessitating new approaches [2,19].
- There is increased awareness of central sensitization, nociplastic pain, and comorbidities (e.g., irritable bowel syndrome and pelvic floor dysfunction) in endometriosis that are not adequately addressed by current treatments. Multimodal care, including pain management, physiotherapy, and psychosocial support, is often lacking [2,3,19].

Current hormonal and surgical treatments for genital endometriosis offer temporary relief but often fail to provide lasting, curative solutions for patients, particularly regarding fertility, pain, and psychosocial well-being issues. Given the high rates of recurrence, side effects, and unmet clinical needs, there is an urgent need for innovative mechanism-based therapies targeting immune, neural, and microbiome pathways.

5. Immunopathogenesis

5.1. Innate Immune Dysfunction

Studies have highlighted immune dysfunction as a key factor in the development of genital endometriosis. Once considered an estrogen-dependent gynecological condition, endometriosis is now recognized as a chronic inflammatory disease with disrupted innate and adaptive immune systems, which support ectopic endometrial tissue survival [23–26].

Normally, immune cells such as macrophages and NK cells remove refluxed endometrial fragments from the peritoneal cavity. However, in endometriosis, these immune cells exhibit altered numbers and functional deficiencies. Peritoneal macrophages increase but show reduced phagocytic ability and adopt a pro-inflammatory, M1-like phenotype, releasing cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α) that enhance inflammation and promote lesion growth [23–26]. NK cells exhibit decreased cytotoxic activity, allowing ectopic endometrial implants to evade immune clearance [24, 27, 28]. Abnormal activity of Tregs and Th17 cells shifts the immune environment toward lesion formation, angiogenesis, and tissue invasion [23,24,29] (**Table 1**).

5.2. Adaptive Immune Dysregulation

Immune dysregulation in the endometrium affects systemic immune responses and the endometrial tissue. Studies have shown abnormal activation of immune cell subtypes, including DCs, B-cells, and regulatory T cells, in the eutopic endometrium and the circulating immune system [23,26,28]. The local cytokine environment shows increased pro-inflammatory cytokines, including TNF-α and interferon-gamma, and Th2-associated cytokines, including interleukin-4 and IL-10, highlighting complex immune activation and suppression that distinguishes endometriosis from normal responses [23, 29]. Immune deficiencies allow endometrial fragments to implant and trigger chronic inflammation. This pro-inflammatory environment promotes nociceptor activation and neuroangiogenesis, which are linked to pain and pelvic symptoms [23, 24, 26]. Immune-related changes in endometrial receptivity and cytokine balance contribute to infertility in patients with endometriosis [26]. The microbiome has a significant influence on the immunopathogenesis of endometriosis. The genital and gut microbiota regulate estrogen metabolism, activate immune cells, and drive inflammation, thereby affecting disease progression [5,8,30]. Microbial dysbiosis can exacerbate immune dysfunction and create conditions conducive to the development of endometriotic lesions [5,30].

Table 1. Immune cell dysfunctions and their roles in genital endometriosis.

Immune Cell Type	Dysfunction/Alteration	Key Mediators/Markers	Consequences
Macrophages	Increased number, reduced phagocytosis; M1 polarization	TNF-α, IL-6, VEGF, TGF-β, MMPs	Promotes inflammation, angiogenesis, and pain
DCs	Immature phenotype, impaired antigen presentation	↓ CD83, ↑ CD1a, IL-10, TGF-β	Inadequate T cell activation and immune evasion
NK Cells	Decreased cytotoxicity; upregulation of inhibitory receptors	↓ Perforin, ↑ KIR2DL1, NKG2A	Impaired clearance of ectopic cells and lesion survival
Tregs	Increased numbers in peritoneal fluid and lesions	IL-10, TGF-β	Immune suppression, angiogenesis, and lesion tolerance
Th17 Cells	Increased numbers and IL-17 production	IL-17, IL-23, IL-6	Promotes inflammation, fibrosis, and angiogenesis
B-Cells	Aberrant activation; production of autoantibodies	ANA, anti-endometrial Ab, BAFF	Autoimmunity, infertility, and tissue damage

Note: DCs: Dendritic cells; NK cells: Natural killer cells; Th17: T helper 17 cells; Tregs: Regulatory T cells; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; VEGF: Vascular Endothelial Growth Factor; TGF-β: Transforming Growth Factor-beta; MMPs: Matrix Metalloproteinases; IL-10: Interleukin-10; IL-17: Interleukin-17; IL-23: Interleukin-23; ANA: Antinuclear Antibodies; Ab: Antibodies; and BAFF: B-cell Activating Factor.

6. Innate Immune Dysfunction

Genital endometriosis is influenced by disruptions in innate immunity, with macrophages, DCs, and NK cells playing key roles. These cells undergo changes that create a pro-inflammatory, tolerogenic environment that supports ectopic endometrial tissue survival and proliferation.

6.1. Dysregulated Macrophage Activity

In women with endometriosis, the number of peritoneal macrophages increases in the peritoneal fluid and lesion sites [23,25]. These macrophages exhibit dysfunction, with reduced phagocytosis and a shift to a pro-inflammatory M1 phenotype, rather than effectively removing endometrial fragments. This leads to increased secretion of TNF-α, IL-6, vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and matrix metalloproteinases (MMPs) [23,25,31]. These cytokines and growth factors promote angiogenesis, matrix remodeling, neural infiltration, and inflammation in endometriotic lesions. This macrophage-driven environment supports lesion vascularization and innervation, contributing to pain and lesion viability [23–25].

6.2. Aberrant Dendritic Cell Function

DCs, which are primarily involved in antigen processing and bridging immunity, show variations in endometriosis. Studies have revealed higher concentrations of immature DCs (CD1a+) in the eutopic endometrium and endometriotic lesions, whereas mature DCs (CD83+) are reduced [23,32]. The abundance of immature DCs indicates disrupted maturation, leading to inadequate T cell responses [23,32]. This creates immune tolerance, allowing endometrial cells to form lesions. DCs release proangiogenic factors that sustain these lesions [23,31]. This DC-driven immune dysregulation is crucial for lesion persistence and pain [32].

6.3. Impaired Natural Killer Cell Cytotoxicity

NK cells are innate immune cells that destroy abnormal or foreign cells, including misplaced endometrial cells. Studies have shown reduced cytotoxic function of NK cells in peritoneal fluid and endometrial tissue [23,27,31]. This occurs due to increased expression of inhibitory receptors, changes in the expression of activating receptors (NKG2D), and the production of immunosuppressive cytokines, such as IL-10 and TGF-β, within the lesion microenvironment [23,27,29]. Research has shown lower lytic activity of peritoneal and endometrial NK cells in affected women than in controls [23,27]. This immune defense breakdown contributes to the formation of lesions and disease recurrence. The dysfunction of macrophages, DCs, and NK cells is interconnected within the peritoneal and endometrial immune environment. Their abnormal activity drives the pro-inflammatory and immunosuppressive characteristics of endometriosis [24,31]. This altered environment supports lesion progression, contributing to

chronic pain and infertility [24,31]. These innate immune irregularities facilitate interactions with adaptive immunity, resulting in persistent disease.

7. Pathogenic Role of Macrophages

Macrophages are key elements of the innate immune system that become dysregulated in genital endometriosis, contributing to the immunopathogenesis of the disease. These cells are present in greater numbers in the peritoneal fluid and endometriotic lesions than in healthy individuals; however, they exhibit functional and phenotypic abnormalities that undermine their homeostatic and protective functions [25,33,34].

7.1. Reduced Phagocytic Function

In normal physiology, macrophages serve as essential scavengers by identifying and removing ectopic endometrial fragments that enter through retrograde menstruation, preventing their abnormal implantation. However, in women with endometriosis, macrophages show diminished phagocytic capability due to changes in surface receptor expression, such as CD36 and CD204, along with influences from peritoneal environment signals [25,35]. This deficiency allows refluxed endometrial cells to evade clearance, facilitating their attachment and survival, which is crucial for lesion formation [27,33].

7.2. Polarization Toward a Pro-Inflammatory M1 Phenotype

In the peritoneal cavity and lesions, macrophages exhibit an M1-like phenotype, marked by classical activation and production of pro-inflammatory mediators such as TNF-α, interleukin-1β (IL-1β), IL-6, and inducible nitric oxide synthase [23,25,31]. This pro-inflammatory state sustains inflammation, which is essential for lesion growth and maintenance. M1 macrophages release matrix metalloproteinases (MMP-2 and MMP-9) that break down extracellular matrix components, promoting invasion and tissue remodeling necessary for lesion expansion [27,36].

7.3. Secretion of Cytokines, Growth Factors, and Neurotrophins

Activated macrophages produce pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, macrophage migration inhibitory factor, and angiogenic factors, including VEGF and TGF-β [27,34,35]. These substances promote neovascularization for lesion survival, activate immune cells, and create a microenvironment that supports chronic inflammation. Neurotrophins from macrophages facilitate neural infiltration and sensitization within lesions, contributing to endometriosis-associated pelvic pain [34]. These dysfunctional macrophage activities create a self-perpetuating cycle: the failure to clear ectopic endometrial cells enables their persistence, while pro-inflammatory polarization promotes lesion vascularization, fibrosis, and pain [27,33]. This maladaptive response interacts with other immune cells and the altered peritoneal environment, furthering immune dysregulation [27,33]. Recent findings indicate that macrophages identify ectopic endometrial tissue as an injury and initiate processes that promote disease progression [27]. This pathogenic involvement makes macrophages potential treatment targets for restoring phagocytic activity, adjusting polarization, and inhibiting cytokine pathways to interrupt the inflammatory cycle in genital endometriosis [25,37].

8. Dendritic Cell Dysfunction

DCs are antigen-presenting cells that connect innate and adaptive immunity by capturing, processing, and presenting antigens to T cells, which triggers immune responses or maintains tolerance [38,39]. In genital endometriosis, the accumulation of immature DCs with impaired antigen presentation is a key immunopathogenic feature. This buildup contributes to local immune tolerance and chronic inflammation, thereby supporting lesion persistence.

8.1. Impaired Antigen Presentation and Dendritic Cells Immaturity

Women with endometriosis show increased immature DCs in both the eutopic endometrium and ectopic lesions. These cells have high CD1a and low or absent expression of maturation markers CD83, CD80, and CD86 [32]. This immature state hampers antigen processing and presentation via MHC class II molecules, leading to insufficient CD4+ helper T cell activation and inadequate cytotoxic T lymphocyte priming. This creates a tolerogenic environment, allowing ectopic endometrial cells to evade immune detection in the peritoneal cavity [23,32].

8.2. Microenvironmental Factors Promoting Dendritic Cells' Tolerogenicity

The peritoneal and lesion microenvironments in endometriosis contribute to DC immaturity by increasing immunosuppressive mediators such as IL-10, TGF-β, and prostaglandin E2, which impair DC maturation and function [24,40]. IL-10 and TGF-β restrict the upregulation of costimulatory molecules required for T cell activation, promoting a tolerogenic DC phenotype that enhances immune suppression. These cytokines also induce DCs to secrete pro-angiogenic factors, such as VEGF, which supports neovascularization, a process essential for lesion growth and maintenance [24,34].

8.3. Functional Impairments in Dendritic Cell Activity

In endometriosis, immature DCs show reduced antigen uptake, impaired MHC peptide loading, and reduced movement to lymphoid organs, failing to trigger adaptive immune responses [38,39]. This dysfunction disrupts immune activation, leading to ineffective targeting of ectopic endometrial tissues. Tolerogenic DC populations promote Treg differentiation, altering the immune environment to support lesion persistence [23,41]. Changes in DC phenotype create an immunological environment in genital endometriosis that impairs antigen presentation and promotes immune tolerance. Chronic inflammation supports lesion persistence, causing pelvic pain and infertility [23,32]. Given their key functions, improving DC maturation and antigen presentation is a promising therapeutic approach. Strategies that promote DC maturation can restore immune monitoring and reduce lesion progression [41,42].

9. Natural Killer Cell Dysfunction

NK cells function as innate immune effectors, swiftly identifying and destroying abnormal, infected, or misplaced cells without prior sensitization. In genital endometriosis, a chronic inflammatory condition marked by abnormal endometrial tissue implantation, NK cells perform immune surveillance within the peritoneal cavity and target refluxed endometrial fragments. Nonetheless, evidence indicates that NK cell dysfunction, characterized by diminished cytotoxicity and predominant inhibitory receptor signaling, significantly contributes to the immunopathogenesis of this disease.

9.1. Reduced Cytotoxicity

In women with endometriosis, NK cells show reduced cytotoxic activity in the peritoneal fluid, marked by lower levels of perforin and granzyme B, with decreased interferon-gamma production, which supports anti-endometriotic immunity [24,43,44]. This decline hinders the ability of NK cells to eliminate ectopic endometrial cells, aiding lesion formation. The peritoneal environment contains immunosuppressive factors, including TGF-β1, IL-6, IL-10, and prostaglandin E2, which inhibit NK cell activity. Platelet-derived TGF-β1 reduces NKG2D receptor expression on NK cells, while IL-6 suppresses granzyme B and perforin through SHP-2 signaling, and blocking IL-6 can restore NK cytotoxicity *in vitro* [43]. These findings highlight how the lesion microenvironment reduces NK cell function.

9.2. Inhibitory Receptor Profiles

NK cell activation depends on signals from activating receptors, such as NKG2D, NKp30, and NKp46, and inhibitory receptors, such as killer-cell immunoglobulin-like receptors and CD94/NKG2A. In endometriosis, this balance shifts towards inhibitory signaling. NK cells from women with the condition show increased inhibitory receptors, including KIR2DL1 and NKG2A [44–46], which intensify negative regulation. Ectopic endometrial cells present non-classical MHC class I molecules, HLA-G and HLA-E, which interact with inhibitory receptors to prevent NK cell degranulation and cytokine release, aiding immune evasion [44,46]. This interaction inhibits NK-mediated clearance. The downregulation of activating receptors, such as NKG2D, driven by TGF-β and other factors, reduces NK cell responsiveness and compromises cytotoxic function [44,45]. The result is a functionally compromised NK cell phenotype that allows ectopic tissues to persist.

9.3. Functional and Clinical Implications

The reduced cytotoxic function of NK cells and increased expression of inhibitory receptors are crucial in the immune system's inability to eliminate ectopic endometrial tissue. This compromised surveillance enables lesion

implantation, persistent inflammation, and angiogenesis, indicating disease progression [24,44]. Furthermore, NK cell abnormalities may disrupt reproductive functions by affecting endometrial immune regulation, hindering trophoblast invasion, and reducing uterine receptivity, thus linking immune dysfunction to endometriosis-associated infertility [23,36].

9.4. Therapeutic Perspectives

Several therapeutic approaches targeting NK cell dysfunction in endometriosis have been explored. These include blocking immunosuppressive cytokines, such as TGF-β and IL-6, to restore NK cytotoxic molecules [43,45,47] and interrupting inhibitory receptor ligand interactions using antibodies against HLA-G or inhibitory killer-cell immunoglobulin-like receptors [44,47]. The adoptive transfer of activated or engineered NK cells shows promise but requires further validation of safety [38]. Studies on cancer immunotherapy have shown that allogeneic NK cells lacking inhibitory receptor ligands for host MHC exhibit enhanced cytotoxicity through "missing self" recognition, suggesting that KIR ligand incompatibility could improve NK cell responses against endometriotic lesions [48,49].

10. Treg/Th17 Imbalance in the Adaptive Immune Dysregulation

In genital endometriosis, adaptive immune system dysregulation is characterized by a disrupted equilibrium between Tregs and Th17 cells, two $CD4^+$ T cell subsets with contrasting roles. This disruption maintains ectopic lesion survival and fosters inflammation in the peritoneum.

10.1. Regulatory T Cells

Tregs, identified by $CD4^+CD25^+FOXP3^+$ markers, maintain peripheral tolerance by curbing immune responses and preventing autoimmune conditions. In endometriosis, Tregs occur at higher concentrations in the peritoneal fluid, eutopic endometrium, and ectopic lesions, creating immunosuppression that hinders the removal of misplaced endometrial cells [23,24]. These cells release IL-10 and TGF-β, which dampen immune responses and promote angiogenesis through VEGF induction, thereby supporting lesion growth [24]. This heightened Treg activity promotes immune tolerance to ectopic endometrial tissue and lesion persistence.

10.2. T Helper 17 Cells

Th17 cells ($CD4^+ROR\gamma t^+$), which produce the pro-inflammatory cytokine interleukin-17 (IL-17), are found in higher numbers in the peritoneal cavity and endometriotic lesions [24, 50]. IL-17 facilitates neutrophil and macrophage recruitment and activation, enhances MMPs and chemokine (CXCL1 and CXCL8) expression, and promotes angiogenesis. These actions intensify inflammation, tissue remodeling, and fibrosis, contributing to disease progression [24,50]. Increased IL-17 and interleukin-23 (IL-23) levels in the peritoneal fluid and serum are positively associated with endometriosis severity in women, highlighting Th17 cells' pathogenic role.

10.3. Cytokine Regulation of TREG/TH17 Differentiation

$CD4^+$ T cells transform into Tregs or Th17 cells based on the cytokine environment shaped by TGF-β and pro-inflammatory signals. TGF-β alone induces $FOXP3^+$ Treg development, whereas its combination with IL-6, IL-1β, or interleukin-21 promotes Th17 differentiation via RORγt expression [51–53]. In endometriosis, peritoneal fluid levels of IL-6, IL-1β, and IL-23, as well as inflammatory agents, support Th17 development while maintaining Treg expansion [23,50,52]. IL-6 inhibits TGF-β-driven Treg induction and enhances Th17 polarization, thereby disrupting the balance between Treg and Th17 in endometriosis [52].

10.4. Hormonal Effects on the Treg/Th17 Axis

Steroid hormones significantly shape the immune axis. Estrogen, a major factor in endometriosis, plays context-dependent roles in modulating Treg and Th17 cells by affecting cytokine signaling and transcriptional pathways vital for lineage commitment. It enhances Treg cells' survival and function while promoting Th17 differentiation through estrogen receptor signaling [24,50]. Progesterone resistance, a characteristic of endometriosis, disrupts T cell differentiation and the cytokine environment, worsening the Treg/Th17 imbalance and aiding disease persistence [50].

10.5. Clinical Implications of the Treg/Th17 Imbalance

A functional shift in the Treg/Th17 balance creates complex pathological effects. Increased Tregs impair the immune system's ability to clear ectopic endometrial cells, allowing for immune evasion. An elevated Th17 response promotes inflammation, blood vessel formation, scarring, and pain. This imbalance impacts fertility, as disrupted immune tolerance and inflammation reduce the endometrium's ability to receive and implant embryos [23,24].

10.6. Therapeutic Strategies to Restore Immune Balance

Addressing the Treg and Th17 cell imbalance is a promising therapeutic strategy. Studies have shown that blocking IL-6 and IL-17 pathways can restore differentiation balance and reduce lesion inflammation [52]. Immunomodulatory substances, such as retinoic acid, suppress IL-6–dependent Th17 differentiation while promoting Tregs [51]. Vitamin D and STAT3 pathway interventions may enhance these effects [54,55]. These strategies aim to reduce inflammation and improve immune monitoring and fertility outcomes of the patients.

11. B-Cell Dysfunction and Autoantibody Production

Adaptive immune dysregulation in endometriosis involves aberrant B-cell activation and the presence of various autoantibodies, indicating a breach of self-tolerance and features shared with autoimmune diseases. Although endometriosis is not classified as a classical autoimmune disorder, a significant proportion of affected women exhibit circulating and local autoantibodies reflecting dysregulated humoral immunity and chronic inflammation.

11.1. Aberrant B-Cell Activation and Autoantibody Types

Multiple classes of autoantibodies have been described in patients with endometriosis. Antinuclear antibodies, markers of autoimmune activity, are more prevalent in these women, suggesting immune activation and a predisposition to autoimmunity [56,57]. Anti-endometrial antibodies targeting endometrial antigens are frequently detected and linked to impaired endometrial receptivity, which interferes with embryo implantation [56,58]. Antiphospholipid antibodies are more common in patients and are correlated with thrombotic events and pregnancy loss, similar to anti-phospholipid syndrome [47,48]. Autoantibodies against ovarian and sperm antigens have been reported to affect fertility by targeting gametes and ovarian function [57,59].

11.2. Cytokine Environment Supporting Autoimmunity

These autoantibodies arise in the peritoneal environment with elevated pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and BAFF. BAFF is markedly upregulated in the serum and peritoneal fluid of women with endometriosis and supports B-cell survival, maturation, and class-switch recombination, thereby enabling autoreactive clones [24,60]. Within endometriotic lesions, ectopic lymphoid-like structures enable local germinal center reactions and autoantibody production [57,60]. Chronic antigenic stimulation by ectopic endometrial debris sustains humoral autoimmunity.

11.3. Pathogenic Effects of Autoantibodies

Evidence suggests that multiple mechanisms are involved in autoantibody pathogenicity. Autoantibodies against intracellular proteins serve as diagnostic markers with indirect roles, whereas those recognizing extracellular antigens exert direct pathogenic effects by interfering with antigen function or mediating complement-dependent cytotoxicity [61]. In endometriosis, immune complexes may activate complement pathways, amplifying inflammation and tissue damage, as shown by complement dysregulation in endometriosis and associated ovarian cancer [62]. Autoantibodies can impair the immune clearance of ectopic endometrium by masking antigens or hindering phagocytosis, promoting lesion survival [57]. Autoimmune targeting of reproductive tissues compromises fertility by disrupting fertilization and implantation [56,57].

11.4. Clinical and Therapeutic Implications

Autoantibody testing is not routinely used for endometriosis diagnosis due to limited specificity, but may indicate the risk of concomitant autoimmune disorders, which are more prevalent in affected patients [56,57].

B-cell modulation strategies have gained interest, with BAFF inhibition and B-cell depletion via anti-CD20 antibodies showing efficacy in autoantibody-mediated diseases, representing potential treatments for severe endometriosis [60,61]. Immunomodulatory therapies that restore immune tolerance require further investigation.

11.5. Cytokine-Mediated Adaptive Immune Dysregulation

In endometriosis, disrupted adaptive immune responses are associated with changes in the cytokine environment, particularly IL-6, TNF-α, and IL-10. These cytokines regulate the equilibrium between pro-inflammatory and immunosuppressive reactions. They influence T cell polarization, B-cell function, and immune cell activity, thereby affecting lesion formation, persistence, and symptoms.

11.6. Interleukin-6

IL-6 acts as a pro-inflammatory cytokine and immune regulator and is found at elevated levels in the serum, peritoneal fluid, and endometriotic lesions [43,63]. It works with TGF-β to drive naïve $CD4^+$ T cells into Th17 cells, which produce IL-17, a cytokine linked to neutrophil recruitment and angiogenesis, aiding in lesion invasiveness [64,65]. IL-6 suppresses Treg differentiation, favoring inflammation and reducing immune tolerance [63]. IL-6 promotes B-cell survival and autoantibody production by upregulating the B lymphocyte stimulator [60]. High IL-6 levels are inversely related to NK cell cytotoxicity, downregulating granzyme B and perforin through SHP-2 modulation, and hindering ectopic tissue clearance [43]. These mechanisms create a pro-inflammatory adaptive immune environment that promotes lesion growth.

11.7. Tumor Necrosis Factor-Alpha

TNF-α is a key pro-inflammatory cytokine produced by activated macrophages and endometrial stromal cells in lesions [57,59]. It promotes cell growth, survival, and blood vessel formation through the VEGF and aids in extracellular matrix breakdown by enhancing MMPs [57]. This cytokine boosts Th1 and Th17 cell responses, sustaining chronic inflammation and contributing to progesterone resistance, which worsens immune dysregulation and disrupts normal endometrial function. Attempts to therapeutically inhibit TNF-α have yielded inconclusive clinical results, highlighting the complexity of this pathway [57].

11.8. Interleukin-10

IL-10 is a key anti-inflammatory cytokine produced by Tregs, B-cells, and macrophages, with higher concentrations found in the peritoneal cavity of patients with endometriosis [57,63]. IL-10 inhibits pro-inflammatory cytokine production and T cell activation, enabling immune tolerance to ectopic endometrial implants [57]. Increased IL-10 impairs NK and $CD8^+$ T cell function, allowing lesion persistence [43]. This creates an environment in which pro-inflammatory and immunosuppressive signals coexist, maintaining chronic disease.

11.9. Integrated Cytokine Imbalance and Pathological Outcomes

The interaction between IL-6, TNF-α, and IL-10 disrupts adaptive immunity through increased Th17 inflammation and compromised Treg regulation [43,63]. This imbalance leads to inflammation, lesion formation, and fibrosis in endometriosis [65,66]. Elevated IL-6 and TNF-α levels sustain inflammation, while IL-10 enables immune tolerance, hindering lesion clearance but promoting tissue remodeling and pain.

11.10. Clinical Relevance and Therapeutic Opportunities

In clinical settings, cytokine levels indicate disease severity, with IL-6 and IL-10 serving as markers of diagnosis and disease progression [63]. IL-6 receptor blockers, such as tocilizumab, show potential in reactivating NK cells and reducing inflammation, whereas TNF-α inhibitors remain experimental [43,57]. Adjusting IL-10 signaling requires balancing immunosuppression and inflammatory responses. Strategies targeting downstream effects, including IL-17 blockade and B-cell modulation through BAFF inhibition, are emerging as promising methods for immune response [60,64].

12. Emerging Therapeutic Strategies

With advances in immunology and microbiome science, the clinical management of endometriosis is set to undergo significant changes, moving from symptom management to approaches that modify the disease by addressing immune imbalances and systemic factors. Three interconnected areas show promise: microbiome interventions, personalized immunophenotyping therapies, and comprehensive multidisciplinary care.

12.1. Probiotics, Prebiotics, and Microbiome Therapies

Evidence shows an interaction between endometriosis and the microbiome in the gut, reproductive system, and peritoneal environments [67,68]. Dysbiosis, with reduced Lactobacillus and increased pro-inflammatory bacteria, is associated with immune activation, altered estrogen metabolism, and compromised mucosal barrier function, which are crucial in lesion formation and inflammation [62,69]. Short-chain fatty acids from the gut microbiota protect against lesion development by influencing host immune signaling pathways, including G protein-coupled receptors and histone deacetylases [5]. Studies have shown that probiotics, prebiotics promoting beneficial bacteria, and fecal microbiota transplantation reduce lesion size and inflammation [68,70]. Clinical findings suggest that microbiome-targeted therapies may restore immune balance by enhancing Treg populations, reducing pro-inflammatory cytokines, and improving mucosal epithelial function, thereby addressing pelvic and systemic immune issues [62,67]. Future objectives include incorporating microbiome profiling into diagnostic and therapeutic strategies [71]. Implementation requires the standardization of methods and consideration of patient-specific factors, such as age, hormonal status, and antibiotic exposure.

12.2. Personalized Medicine Based on Immune Phenotyping

Endometriosis exhibits immunological diversity through cytokine profiles, T cell subset imbalances (Th17/Treg ratio), and B-cell activation markers [26, 60]. Advanced immune profiling techniques enable patient classification into immunophenotypes that predict disease mechanisms and responses [23,60]. Patients with IL-6-driven inflammation may benefit from IL-6 receptor blockers, such as tocilizumab, whereas those with Th17 predominance may benefit from inhibitors targeting the IL-17 or IL-23 pathway [72]. Patients with humoral autoimmunity may respond to B-cell-depleting therapies (rituximab and belimumab) targeting autoantigens [26,61]. Strategies to enhance Tregs, including low-dose interleukin-2 therapy and agents promoting Tregs differentiation, may help restore immune tolerance [72,73]. Multi-omics data integration with machine learning promises improved patient classification for precise immunomodulation [60].

12.3. Integrative and Multidisciplinary Care

The multifaceted nature of endometriosis, including pelvic pain, infertility, fatigue, and psychological distress, requires care beyond conventional gynecological treatment [62,64]. Multidisciplinary teams with expertise in immunology, reproductive endocrinology, pain management, and mental health can effectively address the factors that affect symptom severity. Lifestyle changes and antioxidant-rich diets can be used with immunomodulatory therapies to lower IL-6 and TNF-α levels [5,71]. Physical rehabilitation and cognitive behavioral therapy help alleviate central sensitization and the psychosocial effects of chronic pelvic pain through neuroendocrine pathways [73]. Given the link between psychosocial stressors and immune dysregulation in endometriosis, stress reduction is essential [73]. Collaborative approaches that combine immune monitoring with patient-reported outcomes enable adaptive treatment strategies for holistic health and quality of life.

13. Discussion

The findings of this review show that genital endometriosis involves significant immunological disruptions, aligning with the findings of the studies included in the analysis. Common observations included increased IL-6, TNF-α, and IL-10 levels, along with a Treg/Th17 imbalance and reduced NK cell cytotoxicity. These findings support the view that endometriosis is an immune-inflammatory disorder rather than a solely hormonal one.

Endometriosis, once viewed as an estrogen-dependent condition, is now understood as a chronic immune-mediated inflammatory disease. Disruptions in innate and adaptive immune functions, including macrophage polarization, immature dendritic cells, reduced NK cell cytotoxicity, Treg and Th17 cell imbalance, and autoantibody

production by B-cells, support the persistence of ectopic lesions [23,24,33]. Elevated cytokine levels, including IL-6, TNF-α, and IL-10, create interactions between inflammation and immune tolerance, contributing to pain, infertility, and chronic disease [74–76]. These immune disruptions, along with oxidative stress and microbiome imbalances, redefine endometriosis as a systemic disorder rather than a localized gynecological issue [5,17].

Studies have shown that while macrophages increase, their phagocytosis is compromised, and they release proinflammatory substances that encourage angiogenesis and nerve infiltration [25,34]. Dendritic cells accumulate but remain immature, hindering antigen presentation and encouraging tolerance [32,37]. Natural killer cells show reduced cytotoxicity due to increased expression of inhibitory receptors, such as KIR2DL1 and NKG2A [43,44]. The adaptive immune system is affected by increased Th17 cells, which lead to proinflammatory reactions, whereas Tregs promote immune tolerance, resulting in inflammation with reduced clearance [16]. Humoral responses show abnormal B-cell activation and higher BAFF levels, leading to autoantibody production, drawing similarities between endometriosis and systemic autoimmune diseases [26,60].

Conventional treatments, such as hormonal suppression and surgery, focus on alleviating symptoms rather than addressing immunopathogenic causes, often resulting in recurrence and pain [20,22]. Recent immunological advancements have opened up new possibilities. Therapies targeting cytokines, including IL-6 receptor blockers (tocilizumab) and IL-17 inhibitors (secukinumab), have shown potential in preclinical and early clinical trials [23, 72]. Strategies targeting B-cell/BAFF (belimumab, rituximab) offer another promising direction for autoantibody-driven diseases [60]. Antioxidants such as N-acetylcysteine, resveratrol, curcumin, epigallocatechin gallate, and melatonin inhibit nuclear factor-κB/signal transducer and activator of transcription 3 signaling, decrease oxidative stress, and reduce lesion size in observational studies [12–15]. Interventions targeting the microbiome, including probiotics, prebiotics, and short-chain fatty acid supplementation, have emerged as methods to restore mucosal balance, reduce inflammatory cytokine levels, and boost Treg activity [67,69,70]. These therapeutic advancements suggest a shift towards mechanism-based management strategies rather than symptom treatment.

Although encouraging, these findings have several limitations. This narrative review used a structured approach; however, the qualitative study selection introduced potential bias. The diversity among human, animal, and *in vitro* models makes direct comparisons challenging. Many potential therapies are supported mainly by preclinical data or small pilot studies, with limited randomized controlled trial evidence supporting their integration into standard care. Microbiome research remains exploratory, involving small sample sizes, varying sequencing techniques, and reproducibility problems. Although immune phenotyping and biomarker-based stratification show promise, they remain experimental and unvalidated for clinical applications.

To address these gaps, multicenter studies combining standardized immune and microbiome assessments with clinical data are necessary. Longitudinal studies are needed to elucidate the temporal connections between immune dysfunction and lesion progression. Predictive biomarkers derived from cytokine patterns, immune cell characterization, and microbial profiles could facilitate precision medicine strategies. Incorporating immune modulation with lifestyle, dietary, and psychosocial interventions is vital for providing comprehensive care. Ultimately, transitioning from symptom alleviation to modifying disease mechanisms is crucial for enhancing the quality of life and reproductive outcomes of women with genital endometriosis.

14. Conclusions

Genital endometriosis is a chronic inflammatory disorder driven by immune dysfunction, with abnormalities in immune cells, increased pro-inflammatory cytokine levels, oxidative stress, and altered genital and gut microbiomes. These immunopathogenic insights show that the condition extends beyond a hormone-dependent gynecological issue, affecting pain, infertility, and recurrence. Current hormonal and surgical treatments provide temporary relief without addressing immunological issues, leading to disease recurrence.

Recent developments have highlighted promising therapeutic strategies targeting immune pathways and oxidative stress, including cytokine inhibitors, B-cell/BAFF modulation, and antioxidant compounds such as N-acetylcysteine, resveratrol, curcumin, epigallocatechin gallate, and melatonin. Approaches targeting the microbiome and precision medicine based on immune phenotyping offer potential new treatments. However, these methods lack long-term data from large-scale trials. Future research should focus on multicenter studies integrating immune and microbial profiling with clinical outcomes and care models combining pharmacologic, lifestyle, and psychosocial interventions.

By shifting from symptom management to mechanism-based therapies, we can potentially alter the progression of endometriosis, reduce its recurrence, and improve fertility and quality of life. The combination of immunology and translational medicine is essential for developing lasting personalized solutions.

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Conceptualization, A.A. and N.A.; methodology, E.Y.; data curation, N.A.; writing—original draft preparation, A.A., E.Y., and Y.V.; writing—review and editing, Y.V. All authors have read and agreed to the published version of the manuscript.

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