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Pathological Interaction Mechanisms between Cervical Mycoplasma and Chlamydia Infections and Endometriosis: Novel Clinical Management Strategies

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Abstract

Endometriosis (EMs), a prevalent chronic inflammatory disease among women of reproductive age, has a global prevalence of 10% - 15% and is closely associated with 30% - 50% of infertility cases. This review systematically examines the epidemiological characteristics and molecular pathogenesis of EMs, establishing for the first time a dynamic interaction model between cervical mycoplasma and chlamydia infections in the pathological progression of EMs. Based on epidemiological correlation analysis, it reveals the spatiotemporal association between genital tract infections and EMs onset. By examining inflammatory pathway interactions, immune dysregulation, and microbiome imbalance, it elucidates the potential infection-inflammation-endometriosis "pathological vicious cycle". Clinically, it innovatively proposes a "dual-track treatment" strategy integrating targeted hormone therapy, precision anti-infective regimens, and combined immune-microbiome modulation. This review constructs a precision prevention and treatment system through a translational medicine perspective. It not only achieves a paradigm shift in diagnosis and treatment from "symptom control" to "etiological intervention" but also provides EM patients with personalized treatment pathways based on molecular subtyping. This breakthrough offers a novel methodological framework for addressing treatment resistance and recurrence prevention in EM.

Keywords

Endometriosis (EMs), Immune Dysregulation, Chronic Inflammation, Mycoplasma and Chlamydia Infections

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1. Introduction

Endometriosis is a common chronic gynecological disorder among women of reproductive age. Clinically, it manifests as the growth of endometrioid tissue outside the uterine cavity, primarily distributed within the pelvic cavity—including the ovaries, fallopian tubes, peritoneum, and bladder surface. Its global prevalence is approximately 10%, rising to 30% - 50% among women with infertility [1]. Symptoms of endometriosis exhibit high heterogeneity, including chronic pelvic pain, menstrual irregularities, infertility, and dyspareunia. These symptoms significantly impact patients' quality of life and mental health [2]. The etiology of endometriosis is complex, and its pathogenesis remains incompletely understood. Current mainstream theories include retrograde menstruation, immune dysregulation, genetic susceptibility, and stem cell mechanisms. Retrograde menstruation is considered the primary source of ectopic endometrial implantation, yet not all women develop endometriosis, suggesting other factors—such as immune dysfunction and inflammatory responses—play crucial roles in disease onset and progression [3]. Concurrently, Mycoplasma and Chlamydia infections of the cervix, as the most prevalent sexually transmitted infections in the female reproductive tract, impact reproductive health through their chronic and insidious nature. These pathogens not only cause chronic pelvic inflammation but are also frequently associated with reproductive disorders, such as tubal obstruction, infertility, and recurrent miscarriage. In recent years, increasing research has focused on the potential interplay between Mycoplasma and Chlamydia infections and endometriosis, particularly at the level of shared inflammatory and immunoregulatory mechanisms.

While *Ureaplasma urealyticum* and *Chlamydia trachomatis* infections are predominantly associated with pelvic inflammatory disease and reproductive disorders, their direct link to endometriosis remains incompletely understood. Some studies suggest these pathogens may interact with endometriosis through shared inflammatory pathways. For instance, Ureaplasma infection significantly upregulates TNF-α and IL-1β expression—inflammatory mediators also demonstrated to be markedly elevated in endometriosis [4]. Similarly, *Chlamydia trachomatis* infection may influence the formation and progression of endometriosis by disrupting mucosal barriers, activating the innate immune system, and promoting inflammatory responses and tissue fibrosis [5]. This review will therefore examine the epidemiological characteristics, potential associative mechanisms, and current clinical interventions regarding endometriosis and cervical Mycoplasma/Chlamydia infections, while also outlining future research directions and clinical management strategies.

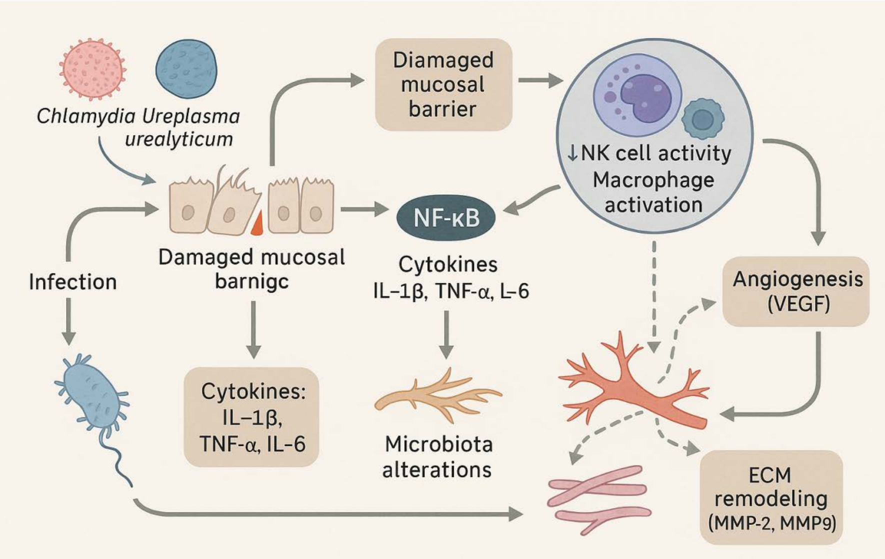
2. Endometriosis

2.1. Pathogenesis of Endometriosis

The early classical theory, the Retrograde Menstruation Theory, posits that during menstruation, fragments of endometrial tissue flow retrograde through the fallopian tubes into the pelvic cavity, implanting at ectopic sites to form lesions. This theory provides a crucial foundation for explaining the origin of ectopic endometrial tissue. However, retrograde menstruation is also common in healthy women, suggesting that retrograde flow alone is insufficient to induce endometriosis. Consequently, researchers further explored that abnormalities in host immune function may be crucial for the implantation and survival of ectopic endometrial tissue. In patients with endometriosis, natural killer (NK) cell activity is significantly reduced, and macrophage clearance function is weakened. This impairs the timely removal of endometrial tissue entering the pelvic cavity, allowing it to survive and form ectopic lesions. Furthermore, ectopic endometrial tissue itself secretes large amounts of pro-inflammatory cytokines (such as IL-1β, TNF-α, IL-6, etc.). These factors further activate local pelvic inflammatory responses and immune system dysregulation, creating an "inflammation-immune abnormality" environment that ultimately promotes disease progression.

Endometriosis exhibits distinct hormone-dependent characteristics. Research indicates that the root cause of significantly elevated estrogen levels within ectopic lesions lies in the abnormally high expression of aromatase (CYP19A1). As the key enzyme converting androgens to estrogens, aromatase becomes hyperactive at lesion sites, continuously converting androgens into estrogens. This creates a localized "high estrogen environment," stimulating persistent growth and proliferation of ectopic endometrial tissue, thereby driving disease progression. Concurrently, ectopic endometrial tissue exhibits resistance to progesterone, known as progesterone resistance. Under normal circumstances, progesterone effectively suppresses endometrial cell proliferation and maintains endometrial homeostasis. However, in this disease, endometrial tissue responds poorly to progesterone, diminishing its antiproliferative capacity and preventing effective control of ectopic endometrial proliferation. The negative effects of estrogen extend beyond promoting endometrial growth. It also activates inflammatory pathways such as the NF-κB pathway, further stimulating local inflammatory responses. This exacerbates tissue damage and immune imbalance, driving disease progression.

Genetic studies indicate familial clustering in endometriosis. Genome-wide association studies (GWAS) have identified multiple disease-associated genetic loci, including WNT4, VEZT, GREB1, and FN1. These genes play crucial roles in regulating endometrial tissue adhesion, migration, and invasiveness. For instance, VEZT gene overexpression enhances ectopic tissue adhesion to surrounding stroma, while GREB1 abnormalities likely accelerate disease progression by disrupting estrogen signaling pathways. Endometriotic lesions exhibit tumor-like characteristics, primarily manifested as abnormal, increased angiogenesis, and enhanced invasiveness. High expression of matrix metalloproteinases (MMP-2 and MMP-9) within lesions promotes degradation of the basement membrane and extracellular matrix, enhancing the migration and invasiveness of ectopic tissue. Concurrently, elevated vascular endothelial growth factor (VEGF) levels in ectopic tissues stimulate neovascularization, supplying essential blood flow and nutrients to sustain lesion survival. This perpetuates ectopic foci, complicating therapeutic management.



2.2. Local Effects of Chronic Inflammation

A prominent pathological feature of endometriosis lies in the ability of ectopic lesions to secrete multiple inflammatory mediators, thereby establishing a persistent chronic inflammatory state within the pelvis. Research indicates that ectopic endometrial tissue secretes pro-inflammatory factors such as IL-1, IL-6, and TNF-*α*. These mediators not only activate macrophages and neutrophils in the pelvis, creating a stable pro-inflammatory environment, but also disrupt normal tissue structures, leading to issues like tubal obstruction and local fibrosis [6]-[8]. Prolonged inflammatory stimulation promotes excessive collagen deposition, triggering fibrosis in the lesions and surrounding tissues. This not only impairs reproductive organ function but also makes complete surgical removal of the lesions difficult [6]. Furthermore, nerve growth factor (NGF) secreted by ectopic lesions can induce local neurosensitization and abnormal neurogenic connections, further exacerbating the patient's chronic pain state.

More notably, persistent chronic pelvic inflammation may compromise the local mucosal barrier and induce immune dysregulation, thereby increasing cervical susceptibility to pathogens. Research indicates that under chronic inflammatory conditions, excessive release of pro-inflammatory mediators and immune imbalance create favorable conditions for Mycoplasma and Chlamydia adhesion and invasion, forming an "infection-inflammation-ectopic" cycle that may exacerbate endometriosis progression [9] [10].

2.3. Microbiome Dysbiosis and Endometriosis

In recent years, the potential impact of the reproductive tract microbiome on endometriosis has garnered increasing attention. Studies reveal significantly reduced microbial diversity in the reproductive tract of endometriosis patients, characterized by decreased dominant bacteria (e.g., lactobacilli) and increased proportions of opportunistic pathogens (e.g., *Ureaplasma urealyticum* and *Chlamydia trachomatis*) [11]. These microbial alterations may influence disease through multiple mechanisms: Ureaplasma and Chlamydia infections can induce massive pro-inflammatory factor secretion, activating inflammatory mediators that directly or indirectly exacerbate endometriotic lesions [12]. Additionally, dysbiosis may compromise mucosal barrier function, impairing the immune system's ability to clear ectopic endometrial tissue.

3. Characteristics of Mycoplasma and Chlamydia Infections

3.1. Characteristics of Cervical Mycoplasma and Chlamydia Infections and Their Relationship with Reproductive System Diseases

Cervical Mycoplasma and Chlamydia infections are the most common sexually transmitted infections (STIs) in the female reproductive system, with *Ureaplasma urealyticum* and *Chlamydia trachomatis* being the primary pathogens.

Ureaplasma urealyticum is a small pathogen lacking a cell wall. Under specific conditions, such as immunosuppression or microecological imbalance, it can transform into a pathogenic bacterium. Characteristics of *Ureaplasma urealyticum* infection include high infection rates and stealthiness. Studies indicate that *Ureaplasma urealyticum* carriage rates among sexually active women reach 40% - 80%, though most infected individuals exhibit no apparent symptoms [11] [12]. Prolonged chronic infection may lead to pelvic inflammatory disease, salpingitis, infertility, and pregnancy complications [13]. Notably, *Ureaplasma urealyticum* induces local immune dysregulation and tissue damage by adhering to epithelial cells and secreting toxic factors and inflammatory mediators. This chronic inflammatory environment within the pelvis may interact with the development and progression of endometriosis: on one hand, persistent inflammation and immune abnormalities provide a "fertile ground" for ectopic endometrial tissue to adhere, grow, and undergo angiogenesis; On the other hand, the preexisting inflammatory background or dysbiosis in endometriosis patients may further increase susceptibility to Ureaplasma infection, thereby forming an "infection-inflammation-endometriosis" cycle.

Chlamydia trachomatis is another common genital tract pathogen. Chlamydia infections are typically asymptomatic, potentially leading to missed treatment windows and progression to chronic pelvic inflammatory disease, tubal obstruction, infertility, and ectopic pregnancy [14]. *Chlamydia trachomatis* survives and replicates within host cells through conversion between the reticulate and primary forms, evading immune recognition while releasing inflammatory mediators that disrupt the genital tract mucosal barrier [15]. Research indicates that *Chlamydia trachomatis* infection may trigger systemic immune responses, further impairing reproductive function [16]. Therefore, in-depth investigation of the bidirectional effects of these pathogens on the reproductive tract microenvironment, immune mechanisms, and endometriotic lesions holds significant importance for maintaining female reproductive health.

3.2. How Anatomical and Physiological Characteristics Make the Cervix a Primary Site for Mycoplasma and Chlamydia Infections

The cervix is a high-risk site for infections in the female reproductive tract, with its unique anatomical and physiological characteristics determining its high susceptibility to pathogens. Located at the junction of the lower and upper reproductive tracts, the cervix possesses a complex anatomical structure and mucosal barrier function, playing a vital role in maintaining reproductive tract health and preventing pathogen invasion. However, under certain specific conditions, these barrier functions may be compromised, thereby increasing the risk of infection.

The mucus secreted by cervical glands forms a vital barrier against ascending infections. Its viscosity and composition undergo dynamic changes throughout the menstrual cycle under hormonal influence [17]. During ovulation, the mucus thins to facilitate sperm passage; by the luteal phase, it thickens to enhance defense. However, pathogens like *Ureaplasma urealyticum* can compromise barrier function by secreting enzymes that degrade mucus components or reducing antimicrobial peptides (e.g., defensins, lysozyme) within it [18].

The squamo-columnar junction of the cervix represents a transitional zone between squamous and columnar epithelium. Here, newly generated cells exhibit high activity but an immature barrier, with loose intercellular connections that facilitate pathogen adhesion and invasion [19]. *Chlamydia trachomatis* and *Ureaplasma urealyticum* bind to epithelial cells via surface adhesion proteins, achieving colonization and replication in this region [20]. Chronic inflammation further damages local epithelium, increasing genetic mutation risk and elevating susceptibility to other cervical pathologies. These dual characteristics render the cervix highly susceptible to pathogens like mycoplasma and chlamydia. Any factor weakening the mucus barrier or altering local epithelial structure—such as hormonal imbalances or microbiome disruption—may heighten infection risk and foster persistent inflammation within the pelvic cavity.

The cervical microenvironment provides multiple conditions conducive to pathogen growth and reproduction. Under normal circumstances, the cervical microecology maintains an optimal acidic pH (approximately 4.0) through the metabolic activity of lactobacilli, thereby inhibiting the growth of most pathogens [21]. However, when microecological imbalance occurs (e.g., reduced lactobacilli or increased proportion of opportunistic pathogens), local pH may rise, compromising the natural anti-infective barrier. For instance, excessive antibiotic use or poor hygiene practices may disrupt the vaginal microbiota, creating favorable conditions for *Chlamydia trachomatis* and *Ureaplasma urealyticum* proliferation. Additionally, the humidity and temperature conditions within cervical tissue support the survival and transmission of these pathogens [22].

Beyond anatomical and microenvironmental factors, the cervical mucosa's local immune characteristics also contribute to its susceptibility. Although the cervical mucosa harbors diverse immune cells (e.g., macrophages and T cells) and antibodies (e.g., IgA) capable of defending against pathogens, certain pathogens possess immune evasion mechanisms. For instance, *Chlamydia trachomatis* suppresses host autophagy to evade immune clearance [23]. *Ureaplasma urealyticum* can weaken the host immune response by mutating surface antigens, thereby establishing persistent infection.

The anatomical and physiological characteristics of the cervix determine its role as a primary site for Mycoplasma and Chlamydia infections. These include its clean structure and the dynamics of its microenvironment [24]. Pathogens achieve invasion and replication by disrupting the mucus barrier, adhering to susceptible areas, altering the local environment, or evading the immune system. These characteristics not only form a crucial basis for infection but also suggest that strengthening barrier protection and regulating the microenvironment in the cervical region are vital for preventing related infections.

3.3. Pathogenesis of Mycoplasma and Chlamydia Infections

Mycoplasma and Chlamydia infections represent the most prevalent pathogenic infections in the female reproductive system, with complex pathogenesis involving multiple pathways and pathological changes. These pathogens colonize hosts through mechanisms including adhesion, invasion, and immune evasion, triggering local and systemic inflammatory responses. They may induce chronic pathological damage, ultimately impairing reproductive function.[25].

Ureaplasma urealyticum, a cell wall-deficient microorganism, relies on surface adhesion proteins to bind to host cells, enabling attachment and colonization on the surface of cervical epithelial cells. Its unique adhesion mechanism allows it to firmly attach to susceptible sites such as the squamocolumnar junction of the cervix, laying the groundwork for subsequent infection [24]. Furthermore, Ureaplasma releases toxic substances during metabolism, such as urease and peroxides. These products not only directly damage host cell membranes but also exacerbate local inflammatory responses by inducing oxidative stress [26]. Simultaneously, Ureaplasma activates the host immune system, significantly upregulating the expression of pro-inflammatory factors like IL-6 and TNF-α, attracting large numbers of immune cells to the infection site. This excessive immune response, while eliminating pathogens, also causes irreversible tissue damage. Particularly, its immune evasion capabilities—such as antigenic variation and suppression of complement activation—enable it to evade immune surveillance long-term, leading to persistent infection and chronic inflammation.

Chlamydia trachomatis achieves infection and proliferation through its unique life cycle [27]. Its elementary body (EB) adheres to host cell surfaces and enters cells via phagocytosis, transforming into a reticular body (RB) intracellularly. It rapidly replicates and forms inclusion bodies. This process not only disrupts host cell structures but also expands infection by releasing inflammatory mediators. The NF-κB signaling pathway activated during *Chlamydia trachomatis* infection significantly increases the secretion of pro-inflammatory cytokines such as IL-1β, IL-8, and IFN-γ. These factors sustain local inflammation through a self-amplifying mechanism [28]. Furthermore, *Chlamydia trachomatis* exhibits potent immune evasion capabilities, such as suppressing host antigen presentation by downregulating MHC-I and MHC-II molecule expression, or evading clearance by interfering with host autophagy pathways. These mechanisms collectively contribute to the persistence and refractory nature of its infection [29].

3.4. The Relationship Between Mycoplasma and Chlamydia Infections and Chronic Inflammation

Whether caused by Mycoplasma or Chlamydia infections, the common pathological feature is tissue damage and functional abnormalities triggered by chronic inflammation [30]. This chronic inflammatory response extends beyond the local infection site, potentially spreading to surrounding tissues and even triggering systemic reactions. At the infection site, the release of numerous pro-inflammatory factors attracts macrophages and neutrophils. While these cells eliminate pathogens, they also release reactive oxygen species (ROS) and reactive nitrogen species (RNS), causing severe damage to host cells [31]. Such fibrosis is a major cause of anatomical abnormalities like tubal obstruction and cervical stenosis, while also significantly increasing the risk of infertility and ectopic pregnancy.

Chronic inflammation further exacerbates the pathological process by promoting angiogenesis and altering the microenvironment. Under persistent inflammatory conditions, vascular endothelial growth factor (VEGF) levels rise significantly, leading to abnormal blood vessel formation. These neovessels not only supply nutrients and oxygen for pathogen survival and spread but may also worsen local hemorrhage and tissue destruction due to increased vascular fragility. Notably, *Chlamydia trachomatis* infection may also trigger systemic immune dysregulation during chronic inflammation, such as elevated systemic IL-1β and IFN-γ levels, thereby affecting other organ functions and potentially correlating with certain autoimmune diseases.

4. Association between Endometriosis and Cervical Ureaplasma and Chlamydia Infections

Endometriosis and cervical ureaplasma and chlamydia infections are two common diseases of the female reproductive system. Although they differ in etiology and presentation, recent studies suggest a potential correlation between the two. Chronic inflammation and immune dysregulation triggered by cervical infections may promote the development of endometriosis, while the chronic inflammatory background in endometriosis patients may also increase susceptibility to pathogen infections.

4.1. Epidemiological Evidence Supporting Correlation

Epidemiological studies indicate significantly elevated rates of Mycoplasma and Chlamydia infections among endometriosis patients, providing preliminary evidence for a potential association. A study of infertile women found Chlamydia infection rates exceeding 30% in those with endometriosis, markedly higher than in women without the condition [32]. The prevalence of Ureaplasma infection is also markedly elevated in endometriosis patients, particularly in the context of chronic pelvic inflammatory disease [33]. This suggests that mycoplasma and chlamydia infections may promote the onset and progression of endometriosis through mechanisms such as inducing inflammation or immune dysregulation.

Higher detection rates of mycoplasma and chlamydia infections are observed in patients with severe endometriosis. This reflects the role of pathogen infection in sustaining a chronic inflammatory environment and suggests a potentially mutually reinforcing vicious cycle between the two. While existing epidemiological data provide important clues, limitations in sample size and inconsistent standards across studies restrict the generalizability of these findings [34].

4.2. Interactions among Inflammatory Pathways

The inflammatory response induced by Mycoplasma and Chlamydia infections is considered a key mechanism linking these pathogens to endometriosis [35]. Mycoplasma and Chlamydia infections are typically accompanied by local and systemic inflammatory responses, manifested as elevated pro-inflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α). These inflammatory mediators are also core pathological factors in endometriosis, supporting the implantation and growth of endometrial cells migrating retrograde into the pelvis by enhancing local angiogenesis and matrix degradation.

Studies indicate that Chlamydia infection significantly amplifies local and systemic inflammatory responses by activating the NF-κB signaling pathway. This mechanism closely parallels the abnormal inflammatory pathways observed in endometriosis patients. This shared inflammatory mechanism may represent a key link in the correlation between the two conditions. Additionally, Ureaplasma infection further exacerbates endometriosis by inducing excessive prostaglandin E2 (PGE2) secretion, thereby promoting vascularization and dissemination of ectopic endometrial tissue [36] [37].

Chronic inflammation not only supports the implantation and growth of ectopic endometrial tissue but also impairs the immune system's ability to clear it. Immune cells activated by the local inflammatory response—such as macrophages and neutrophils—release large amounts of reactive oxygen species and enzymatic substances while phagocytosing pathogens, causing damage to surrounding tissues. This chronic inflammatory environment may provide a crucial foundation for the interaction between the two diseases.

4.3. Impact of Immunomodulation

Both endometriosis and cervical Mycoplasma/Chlamydia infections are closely associated with immune dysregulation. Studies indicate that the immune systems of endometriosis patients exhibit significant immune evasion phenomena, such as reduced natural killer (NK) cell activity and impaired macrophage function. This immune dysfunction facilitates the implantation and survival of endometrial tissue ascending into the pelvic cavity [35].

Mycoplasma and Chlamydia infections further weaken host immune defenses through their immune evasion mechanisms (e.g., antigenic variation, suppression of host MHC molecule expression), establishing a chronic infection state. Furthermore, infection-induced disruption of the mucosal barrier and abnormal immune regulation may provide pathways for ectopic endometrial migration. For example, Chlamydia infection significantly activates matrix metalloproteinases (e.g., MMP-2, MMP-9), promoting extracellular matrix degradation and thereby enhancing the invasiveness of ectopic endometrial tissue. The interaction of these mechanisms may play a key role in the mutual promotion of both diseases.

4.4. Role of Microbiome and Pelvic Environment

Epidemiological evidence first suggests a "infection-first, ectopic-later" temporal association between lower genital tract pathogen infections and endometriosis (EMs): A cohort study in Taiwan Region covering 79,518 cases of cervical/vaginitis patients showed that lower genital tract infections approximately doubled the risk of subsequent EMs (adjusted HR = 2.01, 95% CI 1.91 - 2.12). This finding establishes a population-based foundation for the "pathogen-microbiome-endometriosis" triadic linkage [38].

At the microbial level, a 2024 systematic review and meta-analysis published in PLOS One (8 population studies, n = 1063) indicated that compared to a normal microbiome dominated by lactobacilli, vaginal dysbiosis (BV/moderate BV) was positively correlated with EMs (pooled OR = 1.17), while Lactobacillus-dominant microbiomes may confer protective effects [39]. Metagenomic sequencing further revealed dysbiosis patterns. Studies have shown that EMs patients exhibit significant loss of Lactobacillus iners in the vagina, accompanied by enrichment of opportunistic pathogens such as Anaerococcus, Prevotella, Porphyromonas, and *Ureaplasma urealyticum*, along with increased overall α-diversity. This suggests that after disruption of the lactobacilli-mediated low pH barrier, anaerobic bacteria and mycoplasmas gain a survival advantage [40]. This microbial "displacement" not only elevates local pH and weakens the mucosal barrier but also amplifies pro-inflammatory factors like IL-6 and TNF-α through the Toll-like receptor/NF-κB pathway, providing an inflammatory backdrop for ectopic endometrial cell adhesion, angiogenesis, and matrix remodeling. The causality of pathogen-microbiome interactions in lesion progression was further validated in animal studies: In a mouse endometrioma (EMs) model, vaginal broad-spectrum antibiotic pretreatment or vaginal microbiota transplantation (VMT) from healthy donors significantly reduced lesion volume, decreased Ki-67 expression, and lowered IL-1β/IL-6/TNF-α levels in peritoneal fluid. This effect was closely associated with NF-κB signaling inhibition. These findings suggest that restoring a Lactobacillus-dominant acidic ecosystem or inhibiting NF-κB-mediated inflammatory pathways may represent promising microbiome-based therapeutic strategies for managing EMs.

In summary, vaginal Lactobacillus depletion and pH elevation induced by pathogens such as Mycoplasma and Chlamydia not only compromise the mucosal barrier but also trigger chronic inflammation and angiogenesis signals, creating a "soft landing" environment conducive to endometrial implantation and expansion. Future research may explore novel approaches for preventing and treating EMs through targeted probiotics, vaginal microbiome therapy (VMT), and combined microbiome-immunomodulatory interventions targeting NF-κB.

4.5. Increased Susceptibility to Cervical Mycoplasma and Chlamydia in Endometriosis Patients

The chronic inflammation and immune dysregulation in endometriosis patients may conversely increase their susceptibility to pathogen infections. On one hand, the pro-inflammatory environment of ectopic lesions further activates local inflammatory pathways, exacerbating damage to the cervical epithelial barrier [7] [41]; On the other hand, chronic inflammation may compromise local immune barriers, rendering the cervix more susceptible to Mycoplasma and Chlamydia infections [42] [43]. This susceptibility not only increases the risk of infection occurrence but may also lead to more severe infection manifestations and treatment challenges.

Furthermore, studies reveal significantly reduced diversity of the reproductive tract microbiota and increased proportions of opportunistic pathogens in endometriosis patients, suggesting that susceptibility to infection may be influenced by microbiome imbalance. For instance, reduced lactobacilli may weaken local antimicrobial activity, while proliferation of opportunistic pathogens may intensify inflammatory responses [44]. This complex interplay between the microbiota and the inflammatory environment offers a new interpretive dimension for the association between endometriosis and cervical infection.

5. Discussions

This review analyzes the potential association between endometriosis and cervical Mycoplasma/Chlamydia infections, examining their mutual influences on inflammation, immunity, and the microbiome, and subsequently explores targeted prevention and treatment strategies. Existing research suggests that chronic inflammation and immune dysregulation induced by cervical infections may promote the onset and progression of endometriosis [45]-[47]. Conversely, the local or systemic inflammatory state in endometriosis patients may increase susceptibility to pathogens. However, studies on the specific mechanisms underlying this relationship require further investigation.

Studies confirm that high levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) induced by Mycoplasma and Chlamydia infections also show a significant upward trend in endometriosis patients, suggesting mutual promotion through shared inflammatory pathways [48] [49]. Infection-induced disruption of the mucosal barrier and dysbiosis may also provide a "fertile ground" for the implantation of ectopic endometrial cells within the pelvis, further intensifying the pathological process of endometriosis. While numerous *in vitro* and animal model studies have partially validated that infection exacerbates chronic pelvic inflammation, large-scale population cohort data remain lacking to clarify the true extent of infection's impact on endometriosis pathogenesis.

Our research reveals that endometriosis remains highly challenging to manage clinically. Current interventions often focus on controlling symptoms and progression of individual conditions—such as hormone regulation and surgical approaches for endometriosis, or antibiotic treatment for mycoplasma and chlamydia infections. However, if significant interaction between these two factors exists, treatment strategies must urgently consider their potential mutual influence. Existing literature indicates that concurrently controlling inflammation and correcting microecological imbalances in infected patients may help reduce chronic pelvic inflammation levels, thereby indirectly decreasing ectopic lesion implantation and spread [50]. Combining anti-infective therapy with interventions such as immunomodulation or probiotic supplementation may break the "infection-inflammation-ectopic" cycle, enhancing clinical efficacy and reducing recurrence [51]. However, due to the lack of unified screening criteria and large-scale prospective studies, the specific indications and efficacy evaluation of combined therapy remain to be further established.

The rapid advancement of precision medicine offers new approaches to address these challenges. Through multi-omics technologies such as genomics, transcriptomics, and microbiomics, we can analyze individual differences between endometriosis and cervical infections at the molecular level, identify high-risk populations, and implement personalized interventions targeting their immune, inflammatory, or microbiome characteristics. For instance, patients with specific inflammatory gene variants or dysbiotic microbiomes may benefit more from targeted inflammatory inhibitor therapies or microbiome restoration strategies. Furthermore, developing long-acting anti-inflammatory drugs and novel immunomodulators could significantly enhance treatment efficacy for recurrent or refractory cases.

Although existing studies preliminarily reveal potential links between endometriosis and cervical Mycoplasma or Chlamydia infections, larger-scale epidemiological investigations and high-quality randomized controlled trials are still needed to clarify the causal relationship between the two and the benefits of intervention. The application of multimodal studies (e.g., integrating imaging, molecular diagnostics, and immunological assessments) can further elucidate the intersection of these two diseases at the inflammation-immunity-microenvironment level, providing robust support for early screening and comprehensive prevention strategies. In the future, establishing a unified combined screening process in clinical practice and exploring a comprehensive management model centered on "anti-infection-inflammation control-microecological restoration" may significantly improve patient symptoms and long-term reproductive outcomes.

In summary, endometriosis and cervical Mycoplasma/Chlamydia infections may interact through shared mechanisms involving inflammatory pathways, immune dysregulation, and microecological imbalance. Clarifying their specific associations and implementing combined interventions not only deepens our understanding of endometriosis pathogenesis but also holds promise for delivering more precise and efficient diagnostic and therapeutic pathways for patients. With the integration of more clinical evidence and multidisciplinary technologies, a more comprehensive diagnostic and treatment system may emerge in the field of female reproductive health, offering new opportunities and directions for the prevention and management of such diseases.

The rapid advancement of precision medicine offers hope for the integrated management of endometriosis and cervical infections. Genomics and multi-omics technologies enable deeper exploration of disease heterogeneity across patients, facilitating the identification of high-risk populations and the delivery of personalized prevention and treatment strategies. For instance, patients with specific inflammatory gene mutations or dysbiotic microbiomes may benefit more from targeted inflammatory inhibitor or microbiota restoration strategies than conventional therapies [9] [52] [53]. Furthermore, developing long-acting anti-inflammatory drugs and immunomodulators for recurrent or refractory cases could significantly enhance treatment efficacy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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