

Dual Role of the Endometrial Microbiome-Immune Axis: From Endometrial Homeostasis to Reproductive Disorders

Xiaochuan Yu¹, Yating Zhang², Li Juan Shi², Huali Wang¹

¹Department of Gynecology II, Dalian Women and Children's Medical Center (Group), Dalian, People's Republic of China; ²Graduate School, Dalian Medical University, Dalian, People's Republic of China

Correspondence: Huali Wang, Email wanghl_dl@126.com

Abstract: The homeostasis of the uterine environment is crucial for reproductive health. Recent studies have revealed the complex interplay between the endometrial microbiome, immune system, and the endometrium. Under normal physiological conditions, the microbiome, primarily composed of *Lactobacillus* species, promotes a healthy reproductive environment by maintaining local immune homeostasis, inhibiting the growth of pathogenic microorganisms, and regulating the integrity of the endometrial barrier. However, dysbiosis can abnormally activate local immune responses, disrupting the immune tolerance mechanisms of the endometrium and thereby compromising pregnancy maintenance and overall reproductive health. This study uniquely highlights the role of the endometrial microbiome in modulating immune responses specifically within the uterine environment, a critical factor for reproductive success. Our findings also suggest novel therapeutic strategies targeting microbiome modulation and immune regulation, offering promising avenues for improving reproductive health outcomes. This review aims to explore the regulatory mechanisms of the microbiome-immune axis in both physiological and pathological conditions, with a particular focus on how these interactions specifically influence the uterine environment, while also considering the broader implications of microbiome-immune interactions throughout the entire body. We will analyze its potential role in reproductive health issues and discuss new therapeutic strategies based on microbiome and immune modulation.

Keywords: endometrium, microbiota, immune response, reproductive health, immune tolerance, dysbiosis, recurrent miscarriage, infertility, endometritis

Introduction

The uterine microbiota plays a crucial role in maintaining reproductive health and ensuring successful pregnancy. Traditionally, the endometrium was considered a sterile environment,¹ but recent research has uncovered the presence of unique microbial communities within the uterus. These microbes help regulate local immune responses and maintain the balance of the endometrial environment.^{2,3} When this balance is disrupted, known as dysbiosis, it can trigger immune responses that alter the structure and function of the endometrium, potentially leading to reproductive disorders such as infertility or pregnancy loss. The interaction between the immune system and the uterine microbiota is fundamental for maintaining a healthy uterine environment.⁴ Cells like natural killer (NK) cells, macrophages, and regulatory T cells (Tregs) in the endometrium play key roles not only in defending against pathogens but also in facilitating embryo implantation and sustaining pregnancy.⁵ At the same time, the immune system regulates the microbiota by recognizing and controlling microbial populations. Disruptions in immune function can lead to dysbiosis, which may worsen reproductive health. While current research has revealed the importance of the uterine microbiome-immune axis in regulating endometrial health, the exact mechanisms remain poorly understood. This review aims to provide a new perspective on how these interactions influence reproductive health, emphasizing areas that have been insufficiently explored in past studies. By synthesizing existing knowledge and exploring under-investigated aspects of microbiome-

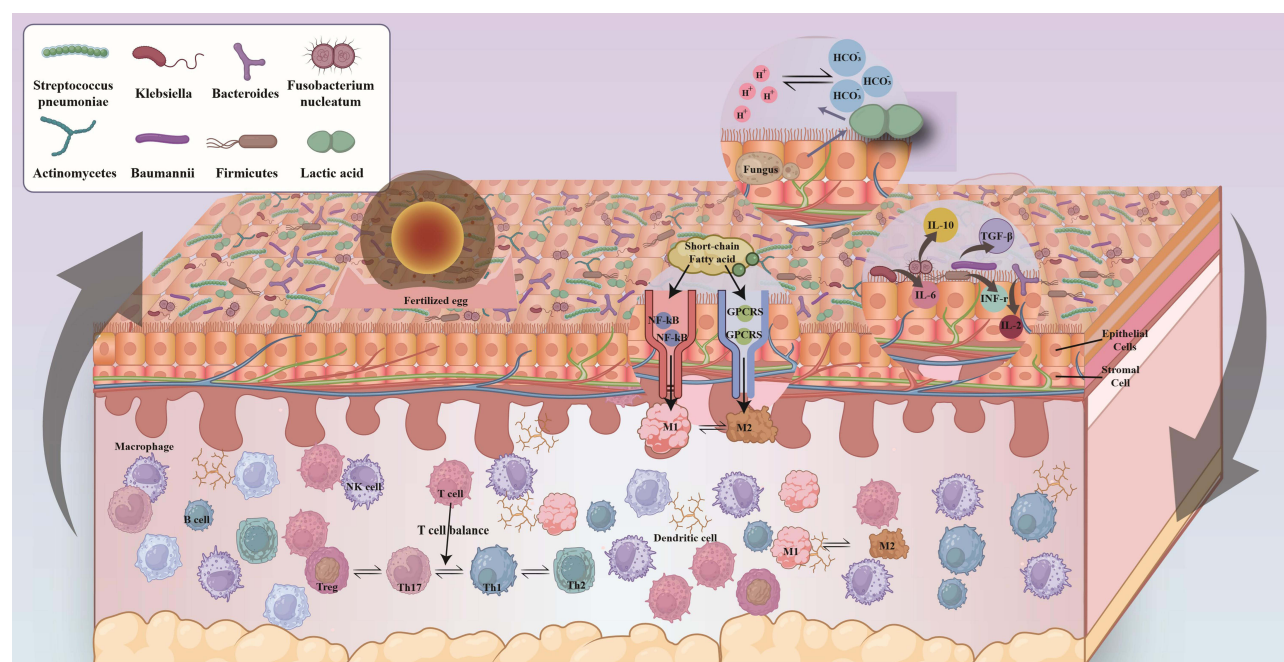


Figure 1 Endometrial Microbiome-Immune Axis: the microorganisms in the endometrium interact with immune cells, establishing a balanced state.

immune interactions, we aim to offer novel insights into how these mechanisms contribute to reproductive dysfunction and potential therapeutic approaches. (ie, Figure 1).

Uterine Microbiota Composition and Function

Composition of the Normal Uterine Microbiota

Recent advancements in 16S rRNA gene sequencing and metagenomic analysis have demonstrated that the uterine cavity is not sterile. Compared to the vaginal and cervical microbiota, the endometrial microbiome exhibits greater uniqueness, complexity, and diversity.⁶ This distinctive microbial composition may be attributed to the endometrium's rich blood supply, cyclic hormonal regulation, direct anatomical connection with the vagina in the lower segment, and indirect connection with the pelvic cavity via the fallopian tubes in the upper segment.

At the phylum level, the endometrial microbiota primarily comprises Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. At the family level, notable families include *Comamonadaceae* (4.92%), *Tissierellaceae* (2.12%), and *Erysipelotrichaceae* (1.6%). At the genus level, the predominant taxa identified are *Lactobacillus* (30.6%), *Pseudomonas* (9.09%), *Acinetobacter* (9.07%), *Vagococcus* (7.29%), *Sphingobium* (5%), *Arthrobacter* (3.89%), *Gonococcus* (3.72%), *Shewanella* (3.38%), unidentified members of the *Pseudomonadaceae* family (2.87%), *Delftia* (2.41%), *Sphingomonas* (1.96%), *Erysipelothrix* (1.06%), *Anaerobacillus*, *Klebsiella*, *Bacteroides*, *Clostridium*, *Flavobacterium*, and other unclassified genera.⁷ At the species level, prevalent microbes include *Escherichia coli*, *Bacteroides fragilis*, *Porphyromonas*, *Helicobacter*, and *Klebsiella*.^{7–10}

However, considerable debate persists regarding the exact composition of the endometrial microbiota, likely due to variability in factors such as volunteer age, menstrual cycle phase, and sampling methods. Nevertheless, numerous studies support that a stable microbiota in the healthy endometrium is crucial for maintaining uterine physiological health and reproductive functionality.

Sola-Leyva et al¹ analyzed RNA sequencing data from 14 endometrial samples (seven from the secretory phase and seven from the proliferative phase) of healthy women. They confirmed significant microbial diversity beyond the genus *Lactobacillus*, identifying *Streptococcus pneumoniae*, *Pasteurella multocida* subspecies, *Klebsiella pneumoniae* subspecies, and *Clostridium botulinum* as notably abundant taxa. Their findings further suggest variability in uterine microbiota composition across different menstrual cycle phases. Additionally, their metatranscriptomic analysis revealed that the

transcriptionally active microbial communities were more abundant during the secretory phase than in the proliferative phase, indicating that *Lactobacillus* may not dominate the endometrial microbiome of healthy young women.

Furthermore, Wang et al,² employing 16S rRNA gene sequencing on uterine samples from 145 women, observed a negative correlation between microbial diversity and age, as age increased, the number of endometrial microbial species decreased, with Firmicutes and Proteobacteria exhibiting the most pronounced variations.

Function of the Uterine Microbiota

The uterine microbiota not only maintains local environmental stability through direct metabolic activities but also interacts closely with the immune system to regulate the endometrial immune response.¹¹ Its primary functions include maintaining local immune homeostasis, contributing to endometrial barrier function and defense mechanisms, and modulating the uterine environment through microbial metabolic products.^{4,5}

In the context of metabolic regulation, *Lactobacillus* species ferment available carbon sources to produce substantial amounts of lactic acid, decrease the pH within the uterine cavity.⁴ This acidification alters the phospholipid composition of pathogen cell membranes, resulting in increased membrane permeability, which compromises the uptake of nutrients and disrupts energy metabolism. Furthermore, the low-pH environment inhibits the activity of key enzymes involved in glycolysis and the tricarboxylic acid (TCA) cycle in pathogens, thereby impeding their energy production and ultimately reducing their growth rate.^{12,13}

In the maintenance of immune homeostasis, *Lactobacillus* activate dendritic cells (DCs), promoting the secretion of interleukin-2 (IL-2), interleukin-10 (IL-10), interferon gamma (IFN- γ), and tumor necrosis factor- α (TNF- α), which in turn modulate the immune response.¹⁴ Additionally, *Lactobacillus* species can suppress the expression of interleukin-12 (IL-12), balance the Th1/Th2 immune response, prevent abnormal endometrial inflammation, and help maintain immune tolerance during pregnancy.¹⁵

With respect to the endometrial barrier, *Lactobacillus reuteri* enhances epithelial barrier function by promoting the expression of tight junction proteins, thereby reducing pathogen invasion into the mucosa.¹⁶ *Lactobacillus rhamnosus* (*L. rhamnosus*) induces the differentiation of Tregs, boosting the anti-inflammatory capacity of the uterine cavity and improving endometrial receptivity.¹⁷ *Lactobacillus johnsonii* (*L. johnsonii*) regulates the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF), enhancing the phagocytic ability of macrophages, accelerating the repair of endometrial inflammation, and reducing the incidence of chronic endometritis (CE).¹⁸

Other dominant bacterial species of the uterine microbiota and their metabolic products also play crucial roles in immune regulation and tissue repair.¹⁹ *Bifidobacterium* species secrete short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which not only regulate immune cell functions through G-protein coupled receptor (GPCR) signaling pathways but also promote angiogenesis to facilitate endometrial regeneration. *Bacteroides fragilis* secretes IL-10, inhibits nuclear factor-kappa B (NF- κ B) signaling, and reduces the release of TNF- α and interleukin-6 (IL-6), thereby alleviating inflammation and promoting cellular repair.²⁰ *Fusobacterium nucleatum* and *Akkermansia muciniphila* secrete interleukin-22 (IL-22), activate the JAK/STAT3 signaling pathway, enhance epithelial cell proliferation, and regulate tight junction proteins and extracellular matrix (ECM) components, thus facilitating endometrial repair. *Streptococcus* species secrete insulin-like growth factor 2 (IGF2), which regulates macrophage M1/M2 polarization through PI3K/Akt and mitogen-activated protein kinase (MAPK) signaling pathways, helping maintain endometrial tissue homeostasis.²¹

In summary, the endometrial microbiota plays a pivotal role in maintaining female reproductive health by modulating local immune homeostasis, enhancing endometrial barrier function, and influencing the uterine environment through microbial metabolites.

Dysbiosis of the Uterine Microbiota and Its Association with Infertility

Dysbiosis, or the imbalance of the uterine microbiota, is a critical factor in the development of conditions such as endometritis and infertility. This section delves into the mechanisms through which dysbiosis impacts the endometrial environment and its subsequent effects on reproductive outcomes.

Endometritis is a chronic inflammatory disease caused by infection and is closely associated with dysbiosis and infertility. It is characterized by persistent inflammation of the endometrium, which may lead to incomplete tissue

repair and damage due to the ongoing inflammatory response. The overgrowth of certain bacteria, such as *Escherichia coli*, anaerobes, and streptococci, is closely related to the development and progression of CE.^{22–24} These bacteria secrete endotoxins and pathogen-associated molecular patterns (PAMPs), which activate natural killer cells, macrophages, and DCs in the endometrium, leading to the release of large amounts of pro-inflammatory cytokines, including interleukin-1 β (IL-1 β), TNF- α , and IL-6, thereby exacerbating the inflammatory response.²⁵ The excessive activation of the immune response due to dysbiosis can inhibit the repair and regeneration of the endometrium, resulting in restricted growth and thinning of the endometrium. When the endometrium is less than 7 mm in thickness and its structure and function are insufficient to support embryo implantation, it is referred to as thin endometrium.²⁶ Studies have shown that dysbiosis in thin endometrium can also impair the function of Tregs, disrupt uterine immune tolerance, and further impede embryo implantation and pregnancy maintenance, leading to infertility and recurrent pregnancy loss (RPL).¹¹ In summary, dysbiosis activates the inflammatory response pathway, leading to impaired endometrial structure and function. Additionally, it disrupts immune tolerance mechanisms, hindering embryo implantation and pregnancy maintenance, collectively contributing to the occurrence of reproductive dysfunction.

Dysbiosis of the Uterine Microbiota and Its Association with Infertility

Uterine microbiota dysbiosis, characterized by alterations in the composition and function of the uterine microbiota, is a key factor in the development of conditions such as endometritis and infertility.

Endometritis is a chronic inflammatory disease induced by infection, closely associated with microbial imbalance and infertility. It is characterized by persistent inflammation of the endometrium, which may impair tissue repair and cause damage due to the ongoing inflammatory response. The overgrowth of *Escherichia coli*, anaerobes, and streptococci is strongly linked to the occurrence and progression of chronic endometritis.^{22–24} These bacteria secrete endotoxins and PAMPs, which activate NK cells, macrophages, and dendritic cells within the endometrium, leading to the release of pro-inflammatory cytokines, including interleukin-1 β , tumor necrosis factor- α , and interleukin-6. This exacerbates the inflammatory response, potentially inhibiting the repair and regeneration of the endometrium.²⁵

A thin endometrium, defined as having a thickness of less than 7 mm during the luteal phase of the menstrual cycle, is another key factor. On one hand, the proliferative and differentiative capabilities of endometrial cells in a thin endometrium may be impaired, reducing endometrial receptivity and hindering embryo implantation.²⁶ On the other hand, dysbiosis in a thin endometrium may disrupt the function of regulatory Tregs, undermining the uterine immune tolerance mechanisms, ultimately obstructing embryo implantation and the maintenance of pregnancy, which can result in infertility and recurrent miscarriage.¹¹

In summary, microbial dysbiosis activates inflammatory pathways, interferes with immune tolerance mechanisms, and impairs the structure and function of the endometrium, ultimately leading to reproductive dysfunction.

Immune Environment of the Endometrium

The immune environment of the endometrium plays a critical role in embryo implantation and pregnancy maintenance, maintaining a delicate balance between effectively defending against pathogen invasion and preventing immune rejection of the fetus or embryo. Dysregulation of this immune environment can lead to reproductive disorders such as infertility, RPL, and endometritis.^{27,28}

The immune environment of the endometrium plays a crucial role in embryo implantation and pregnancy maintenance. It must strike a delicate balance between effectively defending against pathogen invasion and preventing immune rejection of the embryo. Disruption of this balance can lead to reproductive disorders such as infertility, RPL, and endometritis.^{27,28}

The immune environment of the endometrium is composed of various immune cells, primarily T cells, macrophages, and NK cells. These immune cells interact to maintain local immune homeostasis, which plays a critical role in embryo implantation and pregnancy progression.

T cells are key players in the immune response within the endometrium, including helper T cells, cytotoxic T lymphocytes (CTLs), and Tregs. Helper T cells regulate the activity of other immune cells by secreting cytokines such as IL-2, IL-4, and IL-17, while cytotoxic T cells directly recognize and eliminate infected or abnormal cells.

Regulatory T cells play a central role in immune tolerance, suppressing the activity of pro-inflammatory Th1 and Th17 cells by secreting anti-inflammatory cytokines such as IL-10 and TGF- β , thereby reducing the secretion of pro-inflammatory cytokines like IL-6. This process promotes immune tolerance and prevents maternal immune rejection of the embryo.^{29,30}

During pregnancy, the number and activity of Tregs significantly increase. Tregs ensure that the embryo is protected from immune rejection through multiple mechanisms. First, Tregs directly suppress the function of other immune cells, especially by expressing inhibitory molecules such as CTLA-4, which binds to the B7 molecules on antigen-presenting cells, thus inhibiting T cell activation. Additionally, Tregs further suppress the activity of pro-inflammatory Th1 and Th17 cells by secreting anti-inflammatory cytokines like IL-10 and TGF- β , reducing the release of pro-inflammatory factors and maintaining immune tolerance in the local microenvironment. Tregs also enhance immune suppression by inducing functional changes in macrophages and dendritic cells, promoting immune tolerance. Moreover, the increase in the number and activity of Tregs during pregnancy further strengthens immune tolerance, helping the maternal immune system adapt to the presence of the embryo and preventing immune rejection.³¹

Macrophages also play a significant role in the immune environment of the endometrium. Macrophages can be classified into M1 and M2 subtypes. M1 macrophages enhance immune responses by secreting pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6, clearing pathogens, but their overactivation can interfere with embryo implantation, leading to reproductive disorders. In contrast, M2 macrophages suppress immune responses by secreting anti-inflammatory cytokines like IL-10 and TGF- β , supporting immune tolerance and promoting embryo implantation.³² Early in pregnancy, M2 macrophages dominate and contribute to the formation and remodeling of placental blood vessels through the secretion of vascular endothelial growth factor (VEGF), providing essential nutritional support for the embryo.^{32–34}

NK cells are another distinct type of immune cell within the endometrial immune environment. The number of NK cells significantly increases during early pregnancy, accounting for approximately 40%-60% of immune cells.³⁵ NK cells regulate local immune responses by secreting IFN- γ , enhancing immune surveillance and pathogen clearance within the endometrium, and participate in placental vascular remodeling. Through interactions with KIR receptors on trophoblast cells, NK cells inhibit immune responses, preventing fetal rejection.^{36,37} However, overactive NK cells can trigger immune rejection, leading to miscarriage or infertility.³⁸

The establishment of immune tolerance within the endometrium relies not only on direct interactions between immune cells but also on the precise regulation of cytokines, chemokines, and receptor-ligand interactions. Immune suppressive factors such as TGF- β and IL-10 play critical roles in this process. Immune checkpoint molecules such as CTLA-4 and PD-1 inhibit T cell activation and proliferation by binding to their corresponding ligands, preventing excessive immune responses.³⁶ Disruption of these molecular mechanisms may lead to the breakdown of immune tolerance, resulting in pregnancy failure or other reproductive disorders.

In summary, the immune tolerance mechanism of the endometrium is achieved through the complex interactions of immune cells, cytokines, and molecular pathways. Tregs, macrophages, and NK cells, along with their cytokine secretion, receptor-ligand interactions, and cell-to-cell contact, work together to maintain immune tolerance, ensuring that the maternal immune system does not attack the embryo, thus providing the necessary immune environment for successful embryo implantation and pregnancy. Further investigation into these mechanisms will not only help elucidate the pathogenesis of reproductive disorders but also provide a theoretical foundation for developing novel therapeutic strategies.

Microbial Community, Immune Response, and Interaction Mechanisms with the Endometrium

Mechanisms of Microbiota-Mediated Immune Regulation

As we have seen in the previous sections, the uterine microbiota plays a crucial role in maintaining endometrial health. One of the key ways through which the microbiota exerts its influence is by modulating the host immune response. This modulation can occur either directly or indirectly through the production of SCFAs, metabolic intermediates, and signaling molecules.³⁹ A study by Chen et al found that patients with CE dominated by *Leptotrichia* and *Sphingomonas* exhibited significantly higher levels of Th1 cell infiltration.⁴⁰ This may be attributed to microbial

interference with carbohydrate and lipid metabolism in the endometrium, disrupting the Th1/Th2 balance and ultimately hindering embryo implantation. Furthermore, the endometrial microbiota in CE patients can influence the Th1/Th17 ratio through lipopolysaccharides (LPS) signaling. An imbalance in the Th17/Treg ratio adversely affects embryo implantation. LPS has been shown to decrease Tregs while increasing Th17 and Th1 cells.⁴¹ CE patients with elevated Th17 levels also exhibit increased LPS concentrations.⁴⁰ Since LPS is a major component of the outer membrane of Gram-negative bacteria, this further indicates that the endometrial microbiota is closely related to the balance of the number and types of immune cells.⁴²

Feedback Regulation of the Microbiota by the Immune System

The immune system regulates microbial communities through both innate and adaptive immune mechanisms. Innate immunity detects microbe-associated molecular patterns (MAMPs) through pattern recognition receptors (PRRs), initiating inflammatory and antimicrobial responses.^{43,44} PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs), which are expressed by dendritic cells and macrophages and are capable of distinguishing pathogenic from non-pathogenic microbes.^{43,44}

TLRs, as key defense mechanisms against pathogen invasion, play a crucial role in this process: TLR1, TLR2, and TLR6 recognize lipoteichoic acid from Gram-positive bacteria; TLR4 detects LPS from Gram-negative bacteria; and TLR5 recognizes flagellin. Activation of TLRs triggers downstream MAPK and NF- κ B signaling pathways, which regulate the transcription and expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and their receptors. This process promotes cytokine production and upregulates co-stimulatory molecules on antigen-presenting cells, thereby activating T cells and initiating innate immune responses.⁴⁵

Concurrently, the adaptive immune system, through the activation of T cells and B cells, mounts an antigen-specific response that helps maintain the stability and diversity of the microbiota.⁴⁶ The adaptive immune system is highly specific and capable of memory, enabling it to respond to specific microbial antigens. B cells neutralize pathogens by producing antibodies and marking them for clearance by other immune cells. T cells, particularly CD4⁺ helper T cells and CD8⁺ cytotoxic T cells, play a crucial role in regulating microbial communities.⁴⁷ CD4⁺ T cells can differentiate into different subsets such as Th1, Th2, Th17, and Tregs, each with distinct functions.⁴⁷ For instance, Th1 cells produce interferon-gamma (IFN- γ) to participate in cell-mediated immunity against intracellular pathogens; Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13, essential for defending against extracellular parasites and promoting class switching of B cell antibodies; Th17 cells produce IL-17 and play a key role in defending against certain extracellular bacteria and fungi; Tregs help maintain immune tolerance and prevent excessive inflammatory responses.^{48–50} Additionally, the adaptive immune system provides long-term protection through the generation of memory cells, which can rapidly respond to the same pathogen upon re-encounter, further helping to maintain microbial balance.¹¹

In conclusion, innate immunity provides an immediate response to microbial invasion, while adaptive immunity offers more specific and sustained regulation of the microbiota. The synergistic action of B cells, T cells, and memory cells ensures that the immune system can effectively manage microbial communities, maintaining a balanced and healthy microbial environment.

Endometrial Epithelial Regulation of Microbial Communities

Uterine endometrial epithelial cells contribute to antimicrobial defense by secreting interleukin-1 β (IL-1 β), TNF- α , and the antimicrobial peptide LL-37, directly eliminating pathogens and protecting the endometrium.⁵¹ Additionally, epithelial transport proteins such as NCBT, NHE, CFTR, and SLC26A6 regulate bicarbonate (HCO₃⁻) secretion, helping to maintain an alkaline uterine environment.⁵² This pH homeostasis influences the composition and activity of the uterine microbiota, thereby exerting regulatory effects on microbial dynamics.

In summary, the interaction between the microbiota, immune system, and endometrial epithelial cells maintains the homeostasis of the endometrial microenvironment. The microbiota regulates immune cell activity and balance through metabolites and signaling molecules, while the immune system modulates the composition and function of the microbiota via both innate and adaptive immune mechanisms. Endometrial epithelial cells also participate in microbiota regulation

by secreting cytokines and modulating the local pH environment. This dynamic equilibrium is critical for reproductive health, and any disruption can lead to inflammation, immune dysregulation, and reproductive dysfunction.

Dysbiosis and Immune Dysregulation in Reproductive Health Disorders

Reproductive health disorders are a complex group of diseases whose pathogenesis involves multiple factors, with microbial dysbiosis and immune dysregulation playing crucial roles in conditions such as endometritis, intrauterine adhesions, infertility, and recurrent pregnancy loss. These diseases not only impact women's reproductive health but may also lead to severe fertility problems. This section explores the relationship between these conditions and microbial dysbiosis and immune dysregulation in detail.

The development of endometritis is closely related to pathogenic infections and abnormal activation of immune responses. Common pathogenic microorganisms include *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Neisseria gonorrhoeae*.⁵³ These pathogens not only directly cause infection but also stimulate the secretion of high mobility group box 1 (HMGB1) by endometrial stromal cells (HESCs). Elevated HMGB1 levels are released into the extracellular space, triggering macrophage apoptosis and promoting the release of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), thus advancing the progression of endometritis.⁵⁴ Additionally, the infiltration of immune cells into the endometrium further damages embryo implantation. In patients with endometritis, T cells, NK cells, and macrophages are abnormally activated, leading to excessive release of IL-1 β and TNF- α , exacerbating chronic inflammation and inhibiting embryo implantation.⁵⁴ In endometritis, pathogens activate TLRs, triggering a strong inflammatory response that disrupts the normal structure and function of the endometrium.⁵⁵

The pathways of sucrose biosynthesis III (PWY-7347) and sucrose biosynthesis I (SUCCSYN-PWY) are highly active in endometritis. Pathogenic microbes consume intermediates of glycolysis, competing with the host for energy sources, thereby affecting the metabolic homeostasis of the endometrium.⁵⁵ For example, *Chlamydia trachomatis* binds to the host antimicrobial peptide LL-37 via the Pgp3 protein encoded by the host's plasmid, inhibiting the IL-6/IL-8 production induced by LL-37 and reducing neutrophil chemotaxis, thereby suppressing the antimicrobial ability of the endometrium.⁵⁶ Similarly, *Mycobacterium tuberculosis* Rv1768 regulates the NF- κ B-TNF- α signaling pathway and arachidonic acid metabolism via S100A9, impairing the bactericidal ability of macrophages.⁵⁷

In summary, the onset and progression of endometritis involve direct pathogen infection, abnormal immune activation, and disruption of host metabolic homeostasis. These factors intertwine, collectively impacting the normal function of the endometrium, leading to persistent inflammation and impaired embryo implantation.

In patients with intrauterine adhesions (IUA), the likelihood of concurrent endometritis is as high as 64%.⁵⁸ In terms of the microbiome, the overgrowth of pathogenic bacteria activates TLRs, which in turn activate neutrophils, macrophages, and T cells, leading to the release of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α .⁵⁹ This, in turn, inhibits the expression of glycine N-methyltransferase (GNMT) and activates the TGF- β 1/Smad3 signaling pathway, promoting endometrial fibrosis.⁵⁹ Regarding immune regulation, a study by Lv et al demonstrated that in IUA patients, CD301+ macrophages secrete growth arrest-specific 6 (GAS6), which activates the AXL receptor on endometrial stromal cells (HESCs), inducing upregulation of pro-fibrotic genes and activating the NF- κ B signaling pathway, thereby accelerating myofibroblast differentiation. Reducing CD301+ macrophages effectively inhibits endometrial fibrosis in IUA mouse models, improving fertility.⁶⁰ Overall, intrauterine adhesions are closely linked to pathogen infections, abnormal immune activation, and immune dysregulation induced by microbial dysbiosis, leading to endometrial fibrosis and reduced fertility.

Microbial dysbiosis and immune system abnormalities play a key role in the pathogenesis of infertility. A study published in *Microbiome* in 2022 found a significant reduction in beneficial *Lactobacillus* species in the uterine microbiota of infertile patients, while the proportion of *Escherichia coli*, *Streptococcus*, and *Haemophilus parainfluenzae* increased.⁶¹ In the endometrium of infertile patients, there was a marked increase in the number and activity of NK cells, along with elevated levels of interleukin-6 (IL-6), TNF- α , and IFN- γ , which are closely associated with embryo implantation failure.⁶² Additionally, immune-mediated diseases such as antiphospholipid syndrome and rheumatoid diseases may alter the uterine immune environment, further exacerbating infertility.⁶² Infertility is strongly associated with microbial dysbiosis and immune system abnormalities, impacting embryo implantation and reproductive function.

In patients with RPL, the composition of the uterine microbiota undergoes significant changes, with a notable reduction in *Lactobacillus* abundance and an increase in *Gardnerella* and *Prevotella* species.⁶³ Moreover, there are abnormalities in the number and subtypes of decidual natural killer (dNK) cells, which exhibit enhanced immune aggressiveness, disrupting maternal-fetal immune tolerance and leading to miscarriage.⁶⁴ RPL patients also demonstrate a lack of Tregs and a significant increase in the levels of T helper 1 (Th1) cells and their secreted cytokines, including IFN- γ and IL-2.⁶³ This heightened immune response enhances immune rejection of the embryo, thereby contributing to miscarriage. Recurrent pregnancy loss is closely associated with microbial dysbiosis and immune system abnormalities in the uterine microbiota, leading to the disruption of maternal-fetal immune tolerance and miscarriage.

In summary, reproductive health disorders, including endometritis, intrauterine adhesions, infertility, and recurrent pregnancy loss, are closely associated with microbial dysbiosis and immune dysregulation. Pathogen-induced abnormal immune activation and alterations in the microbiota work together to disrupt the normal function of the reproductive system, leading to persistent inflammation, embryo implantation failure, and pregnancy loss.

Clinical Applications and Future Research Directions

Potential of Microbiome Intervention

Currently, clinical treatment for thin endometrium and primarily focuses on anti-inflammatory strategies and restoring the structure of the endometrium. However, there has been relatively less attention on intrauterine immune and microbiota interventions. As a result, some patients with normal endometrial structure are still unable to resolve chronic endometritis, infertility, and recurrent miscarriages.

In recent years, microbiota modulation has garnered increasing attention for improving the uterine environment, particularly in the context of reproductive health disorders such as infertility and recurrent pregnancy loss. Microbiota-targeted strategies, FMT is another emerging intervention that has shown success in treating gut diseases and is currently being explored for its potential in reproductive medicine. Preliminary studies suggest that FMT may regulate the gut-uterus axis, indirectly affecting the uterine microbiota and improving local immune homeostasis. By restoring gut microbiota diversity, FMT may enhance pregnancy rates and reduce the risk of miscarriage.⁶⁵

The potential role of the microbiota in assisted reproductive technologies (ART) has also become an increasingly prominent topic. Recent studies indicate that the success of ART may be closely related to the diversity of the reproductive tract microbiota.⁶⁶ A 2021 study reported a significant positive correlation between endometrial microbiota diversity and the success rate of in vitro fertilization (IVF).⁶⁶ Beyond microbial diversity, the microbiota may also influence reproductive outcomes by modulating immune function and metabolic status.

For instance, Hu et al demonstrated that *Clostridium butyricum* exerts a protective effect on the endometrium in a murine model by alleviating barrier damage and suppressing inflammation in endometritis.⁶⁷ Similarly, studies by Zhang and Xiao showed that ISGylation and Catalpol alleviate LPS-induced inflammatory injury in the endometrium of goats, cattle, and mice by inhibiting activation of the TLR4/NF- κ B pathway.^{68,69} Additional evidence suggests that *C. butyricum* ameliorates *Escherichia coli*-induced endometritis via inactivation of the NF- κ B signaling cascade.⁷⁰ In a murine model of *Staphylococcus aureus*-induced endometritis, *C. butyricum* significantly downregulated the expression of TLR4, p-p65/p65, and p-I κ B/I κ B, thereby suppressing NF- κ B pathway activation and mitigating inflammation.⁷¹

These findings underscore the ability of microbiota modulation not only to reshape local immune responses but also to attenuate inflammatory damage by targeting key immunological pathways such as NF- κ B. Collectively, microbiota-based strategies—including probiotics and FMT—hold substantial potential to improve reproductive health by enhancing the uterine environment and increasing ART success rates. Future research should focus on elucidating the underlying mechanisms of microbiota–host interactions and on developing precision microbiome therapies to optimize fertility and clinical outcomes in reproductive medicine.

Immunomodulatory Strategies

Dysregulation of immune tolerance mechanisms is closely associated with diseases such as recurrent miscarriage (RM) and infertility. Therefore, immunomodulatory strategies targeting the immune system hold promise as potential

therapeutic options for these patients. Studies have shown that restoring Treg cell function can improve pregnancy rates and reduce miscarriage occurrence. A 2023 study demonstrated that the infusion of autologous Treg cells significantly improved pregnancy outcomes in patients with RM.⁷² In 2021, researchers found that adjusting the proportion of Tregs in the immune system could significantly enhance embryo implantation rates and decrease miscarriage rates.⁷³ Additionally, anti-inflammatory drugs and immunosuppressants may serve as adjunctive therapies by inhibiting excessive immune responses and restoring immune tolerance within the uterus.

Immunotherapeutic strategies targeting microbiome dysbiosis also hold significant clinical relevance. In 2024, researchers proposed that restoring microbiome balance through immunotherapy could not only alleviate inflammatory responses but also restore uterine immune tolerance, providing novel approaches for treating infertility and RM.⁷⁴

Conclusion

This review underscores the essential role of the uterine microbiota and immune system in preserving reproductive health, highlighting the critical balance necessary for successful pregnancy. The uterine microbiota, dominated by beneficial bacteria such as *Lactobacillus*, is fundamental in regulating local immune responses, maintaining the endometrial barrier, and supporting a conducive uterine environment. Dysbiosis, or microbial imbalance, disrupts immune tolerance, leading to chronic inflammation and conditions like endometritis, intrauterine adhesions, infertility, and recurrent pregnancy loss.

We also emphasize the key involvement of immune cells, especially regulatory T cells, macrophages, and natural killer cells, in establishing and maintaining endometrial immune tolerance. These cells interact with the microbiota through complex signaling pathways to regulate immune responses that facilitate embryo implantation and sustain pregnancy. Disruptions in these interactions, whether through microbial imbalances or immune dysfunction, can severely impact reproductive health.

Emerging therapies, such as probiotics, fecal microbiota transplantation (FMT), and targeted immunotherapies, offer promising strategies to restore microbial balance and immune tolerance. These interventions have shown potential in improving the uterine environment and enhancing reproductive outcomes.

Future research should focus on exploring the precise mechanisms of microbiota-immune interactions in the uterine environment. Longitudinal multi-omics studies are needed to track microbial shifts during pregnancy and their effects on reproductive health. Additionally, understanding how specific immune cell subsets interact with the microbiota will be crucial for developing targeted therapeutic approaches.

In conclusion, maintaining the balance between the uterine microbiota and immune system is vital for reproductive health. Further interdisciplinary research is necessary to fully exploit the therapeutic potential of microbiome and immune-based interventions to improve fertility and pregnancy success rates.

Declaration of Generative AI in Scientific Writing

No generative artificial intelligence (AI) or AI-assisted technologies were used during the writing process.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Dalian Municipal Guiding Program in the Field of Life and Health (Approval No. 2024ZDJH01PT038). The Third Batch of the President's Fund of Dalian Women and Children's Medical Center (Group) (Approval No.2024-FEJT-YZ-08).

Disclosure

The authors declare that they have no conflict of interest regarding the publication of this article. All authors have no financial or non-financial relationships that may influence the interpretation of the data or the conclusions of the study.

References

1. Sola-Leyva A, Andrés-León E, Molina NM, et al. Mapping the entire functionally active endometrial microbiota. *Hum Reprod.* 2021;36(4):1021–1031. doi:10.1093/humrep/deaa372
2. Wang J, Li Z, Ma X, et al. Translocation of vaginal microbiota is involved in impairment and protection of uterine health. *Nat Commun.* 2021;12(1):4191. doi:10.1038/s41467-021-24516-8
3. Bortolotti D, Soffritti I, D'Accolti M, et al. HHV-6A infection of endometrial epithelial cells affects miRNA expression and trophoblast cell attachment. *Reprod Sci.* 2020;27(3):779–786. doi:10.1007/s43032-019-00102-8
4. Fraszczak K, Barczyński B, Kondracka A. Does lactobacillus exert a protective effect on the development of cervical and endometrial cancer in women? *Cancers.* 2022;14(19):4909. doi:10.3390/cancers14194909
5. Shiroda M, Manning SD. Lactobacillus strains vary in their ability to interact with human endometrial stromal cells. *PLoS One.* 2020;15(9):e0238993. doi:10.1371/journal.pone.0238993
6. Koedooder R, Mackens S, Budding A, et al. Identification and evaluation of the microbiome in the female and male reproductive tracts. *Hum Reprod Update.* 2019;25(3):298–325. doi:10.1093/humupd/dmy048
7. Chen C, Song X, Wei W, et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. *Nat Commun.* 2017;8(1):875. doi:10.1038/s41467-017-00901-0
8. Moreno I, Codoñer FM, Vilella F, et al. Evidence that the endometrial microbiota has an effect on implantation success or failure. *Am J Obstet Gynecol.* 2016;215(6):684–703. doi:10.1016/j.ajog.2016.09.075
9. Fang R-L, Chen L-X, Shu W-S, Yao S-Z, Wang S-W, Chen Y-Q. Barcoded sequencing reveals diverse intrauterine microbiomes in patients suffering with endometrial polyps. *Am J Transl Res.* 2016;8(3):1581–1592.
10. Franasiak JM, Werner MD, Juneau CR, et al. Endometrial microbiome at the time of embryo transfer: next-generation sequencing of the 16S ribosomal subunit. *J Assist Reprod Genet.* 2016;33(1):129–136. doi:10.1007/s10815-015-0614-z
11. Zhu N, Yang X, Liu Q, et al. “Iron triangle” of regulating the uterine microecology: endometrial microbiota, immunity and endometrium. *Front Immunol.* 2022;13:928475. doi:10.3389/fimmu.2022.928475
12. Ferreira R, Nova BGV, Carmo MS, Abreu AG. Mechanisms of action of Lactobacillus spp. in the treatment of oral candidiasis. *Braz J Biol.* 2024;84:e282609. doi:10.1590/1519-6984.282609
13. Zheng Y, Zhao J, Nie X, Chitrakar B, Gao J, Sang Y. Mutual adhesion of Lactobacillus spp. to intestinal cells: a review of perspectives on surface layer proteins and cell surface receptors. *Int J Biol Macromol.* 2024;282(Pt 4):137031. doi:10.1016/j.ijbiomac.2024.137031
14. Mehdizadeh Sari F, Mirkalantari S, Nikoo S, et al. Potential of Lactobacillus acidophilus to modulate cytokine production by peripheral blood monocytes in patients with endometriosis. *Iran J Microbiol.* 2022;14(5):698–704. doi:10.18502/ijm.v14i5.10965
15. Wang W, Feng D, Ling B. Biologia Futura: endometrial microbiome affects endometrial receptivity from the perspective of the endometrial immune microenvironment. *Biologia Futura.* 2022;73(3):291–300. doi:10.1007/s42977-022-00134-3
16. Yi H, Wang L, Xiong Y, et al. Lactobacillus reuteri LRI improved expression of genes of tight junction proteins via the MLCK pathway in IPEC-1 cells during infection with enterotoxigenic escherichia coli K88. *Mediators Inflamm.* 2018;2018:6434910. doi:10.1155/2018/6434910
17. Yang S, Li W, Challis JRG, Reid G, Kim SO, Bocking AD. Probiotic Lactobacillus rhamnosus GR-1 supernatant prevents lipopolysaccharide-induced preterm birth and reduces inflammation in pregnant CD-1 mice. *Am J Obstet Gynecol.* 2014;211(1):44.e1–44.e12. doi:10.1016/j.ajog.2014.01.029
18. Guo J, Cao X, Li Z, et al. Protective effects of engineered Lactobacillus johnsonii expressing bovine granulocyte-macrophage colony-stimulating factor on bovine postpartum endometritis. *Front Vet Sci.* 2024;11:1418091. doi:10.3389/fvets.2024.1418091
19. Bernabe MCM, Fonseca BB, Silva MVC, et al. Equine endometrial bacteria inhibition by metabolite and extracellular vesicles of Lactobacillus acidophilus and lactiplantibacillus plantarum. *Vet Res Commun.* 2025;49(1):61. doi:10.1007/s11259-024-10626-3
20. Putra AK SA, Surono IS. The downregulation of pro-inflammatory cytokine interleukin-6 after oral administration of Lactobacillus plantarum IS-10506 in mice model for endometriosis. *Indian J Animal Res.* 2023;57(5):620–625.
21. X H, Chen W, Zhou X, et al. The therapeutic potential of lactobacillus crispatus for chronic endometritis: a comprehensive clinical trial and experimental investigation. *Probiotics Antimicrob Proteins.* 2024.
22. Zhang H, Zou H, Zhang C, Zhang S. Chronic endometritis and the endometrial microbiota: implications for reproductive success in patients with recurrent implantation failure. *Ann Clin Microbiol Antimicrob.* 2024;23(1):49. doi:10.1186/s12941-024-00710-6
23. Moreno I, Cicinelli E, Garcia-Grau I, et al. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. *Am J Obstet Gynecol.* 2018;218(6):602.e1–602.e16. doi:10.1016/j.ajog.2018.02.012
24. Kitaya K, Takeuchi T, Mizuta S, Matsubayashi H, Ishikawa T. Endometritis: new time, new concepts. *Fertil Steril.* 2018;110(3):344–350. doi:10.1016/j.fertnstert.2018.04.012
25. Khan KN, Fujishita A, Hiraki K, et al. Bacterial contamination hypothesis: a new concept in endometriosis. *Reprod Med Biol.* 2018;17(2):125–133. doi:10.1002/rmb2.12083
26. Ganer Herman H, Volodarsky-Perel A, Ton Nu TN, et al. Pregnancy complications and placental histology following embryo transfer with a thinner endometrium. *Hum Reprod.* 2022;37(8):1739–1745. doi:10.1093/humrep/deac148
27. Robertson SA, Moldenhauer LM, Green ES, Hull ML. Immune determinants of endometrial receptivity: a biological perspective. *Fertil Steril.* 2022;117(6):1107–1120. doi:10.1016/j.fertnstert.2022.04.023
28. Agostinis C, Mangogna A, Bossi F, Ricci G, Kishore U, Bulla R. Uterine immunity and microbiota: a shifting paradigm. *Front Immunol.* 2019;10:2387. doi:10.3389/fimmu.2019.02387

29. Green S, Politis, M, Rallis, KS, Saenz de Villaverde Cortabarría, A, Efthymiou, A, Mureanu, N et al, et al. Regulatory T Cells in Pregnancy Adverse Outcomes: A Systematic Review and Meta-Analysis. *Front Immunol.* **2021**, 10 29;147:12 737862 doi:10.3389/fimmu.
30. Huang N, Chi H, Qiao J. Role of regulatory T cells in regulating fetal-maternal immune tolerance in healthy pregnancies and reproductive diseases. *Front Immunol.* **2020**;11:1023. doi:10.3389/fimmu.2020.01023
31. Robertson SA, Care, AS, Moldenhauer, LM, et al. Regulatory T cells in embryo implantation and the immune response to pregnancy. *Clin Invest.* **2018**, 10 1;128:10 4224–4235 doi:10.1172/JCI122182.
32. Park M, Kim YS, Song H. Macrophages: a double-edged sword in female reproduction and disorders. *Exp Mol Med.* **2025**.
33. Jiang X, Li L. Decidual macrophage: a reversible role in immunotolerance between mother and fetus during pregnancy. *Arch Gynecol Obstet.* **2024**;309(5):1735–1744. doi:10.1007/s00404-023-07364-3
34. Lou Y, Fu Z, Tian Y, et al. Estrogen-sensitive activation of SGK1 induces M2 macrophages with anti-inflammatory properties and a Th2 response at the maternal–fetal interface. *Reprod Biol Endocrinol.* **2023**;21(1):50. doi:10.1186/s12958-023-01102-9
35. Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal–fetal interface in humans. *Nature.* **2018**;563 (7731):347–353. doi:10.1038/s41586-018-0698-6
36. Joo JS, Lee, D, Hong, JY, et al. Multi-Layered Mechanisms of Immunological Tolerance at the Maternal-Fetal Interface. *Immune Netw.* **2024**, 7 15;24:4 e30 doi:10.4110/in.2024.24.e30.
37. Robson A, Harris, LK, Innes, BA et al, et al. Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. *FASEB J.* **2012**, 12 26;12:4876–85 doi:10.1096/fj.12-210310.
38. Liu Y, Li L, Feng T, et al. Abnormal miR-122-5p expression in decidual NK cells and its impact on trophoblast behavior: insights into unexplained recurrent pregnancy loss. *Int J Med Sci.* **2024**;21(14):2824–2836. doi:10.7150/ijms.101865
39. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic T reg cell homeostasis. *Science.* **2013**;341(6145):569–573. doi:10.1126/science.1241165
40. Chen P, Chen P, Guo Y, Fang C, Li T. Interaction between chronic endometritis caused endometrial microbiota disorder and endometrial immune environment change in recurrent implantation failure. *Front Immunol.* **2021**;12:748447. doi:10.3389/fimmu.2021.748447
41. Candelli M, Franza L, Pignataro G, et al. Interaction between lipopolysaccharide and gut microbiota in inflammatory bowel diseases. *Int J Mol Sci.* **2021**;22(12):6242. doi:10.3390/ijms22126242
42. Baker JM, Chase DM, Herbst-Kralovetz MM. Uterine microbiota: residents, tourists, or invaders? *Front Immunol.* **2018**;9:208. doi:10.3389/fimmu.2018.00208
43. Sheldon IM, Bromfield JJ. Innate immunity in the human endometrium and ovary. *Am J Reprod Immunol.* **2011**;66(s1):63–71. doi:10.1111/j.1600-0897.2011.01034.x
44. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol.* **2016**;16(6):341–352. doi:10.1038/nri.2016.42
45. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell.* **2010**;140(6):805–820. doi:10.1016/j.cell.2010.01.022
46. Kabat AM, Pott J, Maloy KJ. The mucosal immune system and its regulation by autophagy. *Front Immunol.* **2016**;7:240. doi:10.3389/fimmu.2016.00240
47. Tilburgs T, Claas FH, Scherjon SA. Elsevier trophoblast research award lecture: unique properties of decidual T cells and their role in immune regulation during human pregnancy. *Placenta.* **2010**;31:S82–6. doi:10.1016/j.placenta.2010.01.007
48. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine.* **2015**;74(1):5–17. doi:10.1016/j.cyto.2014.09.011
49. Saito S, Nakashima A, Shima T, Ito M. REVIEW ARTICLE: th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol.* **2010**;63(6):601–610. doi:10.1111/j.1600-0897.2010.00852.x
50. You P, Chen N, Su L, Peng T, Chen G, Liu Y. Local level of TGF- β 1 determines the effectiveness of dexamethasone through regulating the balance of Treg/Th17 cells in TNBS-induced mouse colitis. *Exp Ther Med.* **2018**;15(4):3639–3649. doi:10.3892/etm.2018.5852
51. Vandamme D, Landuyt B, Luyten W, Schoofs L. A comprehensive summary of LL-37, the factotum human cathelicidin peptide. *Cell Immunol.* **2012**;280(1):22–35. doi:10.1016/j.cellimm.2012.11.009
52. Wang XF, Yu MK, Leung KM, et al. Involvement of Na⁺-HCO₃[−] cotransporter in mediating cyclic adenosine 3',5'-monophosphate-dependent HCO₃[−] secretion by mouse endometrial epithelium1. *Biol Reprod.* **2002**;66(6):1846–1852. doi:10.1095/biolreprod66.6.1846
53. Yan X, Jiao, J, Wang, X, et al. The pathogenesis, diagnosis, and treatment of chronic endometritis: a comprehensive review. *Front Endocrinol (Lausanne).* **2025**, 6 12;16:1603570 doi:10.3389/fendo.
54. Yang G, Zhang Q, Tan J, et al. HMGB1 induces macrophage pyroptosis in chronic endometritis. *Int Immunopharmacol.* **2023**;123:110706. doi:10.1016/j.intimp.2023.110706
55. Chen P, Guo Y, Jia L, et al. Interaction between functionally activate endometrial microbiota and host gene regulation in endometrial cancer. *Front Cell Dev Biol.* **2021**;9:727286. doi:10.3389/fcell.2021.727286
56. Hou S, Sun X, Dong X, et al. Chlamydial plasmid-encoded virulence factor Pgp3 interacts with human cathelicidin peptide LL-37 to modulate immune response. *Microbes Infect.* **2019**;21(1):50–55. doi:10.1016/j.micinf.2018.06.003
57. Liu S, Xie Y, Luo W, et al. PE_PGRS31-S100A9 interaction promotes mycobacterial survival in macrophages through the regulation of NF- κ B-TNF- α signaling and arachidonic acid metabolism. *Front Microbiol.* **2020**;11:845. doi:10.3389/fmicb.2020.00845
58. Wang Z-N, Wang X M-S, Xi X. Clinical evidence of positive correlation between intrauterine adhesions and chronic endometritis: a retrospective study. *Eur Rev Med Pharmacol Sci.* **2023**;27(10):4601–4607. doi:10.26355/eurrev_202305_32467
59. Zeng S, Liu X, Liu D, Song W. Research update for the immune microenvironment of chronic endometritis. *J Reprod Immunol.* **2022**;152:103637. doi:10.1016/j.jri.2022.103637
60. Lv H, Sun H, Wang L, et al. Targeting CD301 + macrophages inhibits endometrial fibrosis and improves pregnancy outcome. *EMBO Mol Med.* **2023**;15(9):e17601. doi:10.15252/emmm.202317601
61. Moreno I, Garcia-Grau, I, Perez-Villaroya, D et al, et al. Endometrial microbiota composition is associated with reproductive outcome in infertile patients. *Microbiome.* **2022**, 1 4;10(1):1 doi:10.1186/s40168-021-01184-w.
62. Xie S, Matsumura Y, Ikemoto Y, et al. Immune dysfunction in female infertility and its role in pregnancy failure. *Ame J Reproduct Immunol.* **2021**;85(5):e13376. doi:10.1111/aji.13376

63. Garmendia JV, De Sanctis CV, Hajdúch M, De Sanctis JB. Microbiota and recurrent pregnancy loss (RPL); more than a simple connection. *Microorganisms*. 2024;12(8):1641. doi:10.3390/microorganisms12081641
64. Zheng Z-M, Shi J-W, Wang L, Li M-Q. NK cells: shielding senescence homeostasis in the decidua during early pregnancy. *Semin Immunopathol*. 2025;47(1):22. doi:10.1007/s00281-025-01048-7
65. Kong Y, Liu Z, Xiao Q, et al. Protective effects of engineered lactobacillus crispatus on intrauterine adhesions in mice via delivering CXCL12. *Front Immunol*. 2022;13:905876. doi:10.3389/fimmu.2022.905876
66. Kadogami D, Nakaoka, Y, Morimoto, Y, et al. Exploratory evaluation of the bacterial load of uterine microbiota: Potential implications for implantation and treatment response in assisted reproductive technology. *J Reproduct Immunol*. 2025, 12 31;173:104830 doi:10.1016/j.jri.2025.104830.
67. Hu X, Guo J, Xu M, et al. Clostridium tyrobutyricum alleviates Staphylococcus aureus -induced endometritis in mice by inhibiting endometrial barrier disruption and inflammatory response. *Food Funct*. 2019;10(10):6699–6710. doi:10.1039/C9FO00654K
68. Zhang H, Wu Z-M, Yang Y-P, et al. 梓醇通过抑制炎症反应和 TLR4/NF-κB 信号通路改善脂多糖诱导的小鼠子宫内膜炎. *J Zhejiang Univ Sci B*. 2019;20(10):816–827. doi:10.1631/jzus.B1900071
69. Xiao J, Li S, Zhang R, et al. ISGylation inhibits an LPS-induced inflammatory response via the TLR4/NF-κB signaling pathway in goat endometrial epithelial cells. *Animals*. 2021;11(9).
70. Mun C, Cai J, Hu X, Zhang W, Zhang N, Cao Y. Clostridium butyricum and its culture supernatant alleviate the escherichia coli-induced endometritis in mice. *Animals*. 2022;12(19). doi:10.3390/ani12192719
71. Liu J, Tang X, Chen L, Zhang Y, Gao J, Wang A. Microbiome dysbiosis in patients with chronic endometritis and Clostridium tyrobutyricum ameliorates chronic endometritis in mice. *Sci Rep*. 2024;14(1):12455. doi:10.1038/s41598-024-63382-4
72. Cai S, Dai, S, Lin, R, et al. The effectiveness and safety of intrauterine infusion of autologous regulatory T cells (Tregs) in patients with recurrent pregnancy loss and low levels of endometrial FoxP3 cells: A retrospective cohort study. *Am J Reprod Immunol*. 2023, 8;90(2):e13735 doi:10.1111/aji.13735.
73. Huang Q, Wu, H, Li, M, et al. Prednisone improves pregnancy outcome in repeated implantation failure by enhance regulatory T cells bias. *J Reprod Immunol*. 2021, 2;143:103245 doi:10.1016/j.jri.2020.103245.
74. Blazheva S, Pachkova, S, Bodurska, T et al, et al. Unlocking the Uterine Code: Microbiota, Immune Cells, and Therapy for Recurrent Reproductive Failure. *Microorganisms*. 2024, 3 9. 12:3 547 doi:10.3390/microorganisms12030547.

International Journal of Women's Health

Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-womens-health-journal>

Dovepress
Taylor & Francis Group