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A Dive into the Invisible: The Vaginal and Endometrial Microbiome in Gynecologic and Obstetric Disorders—A Narrative Review

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Abstract

The human microbiome is increasingly recognized as a key component of women's reproductive health. This narrative review examines the vaginal, endometrial, and gut microbiota and their roles in the pathogenesis of gynecologic and obstetric disorders, with the aim of integrating current evidence into a clinically relevant framework. We review intrinsic (genetic, hormonal, and immunological) and extrinsic (environmental, lifestyle, and pharmacological) factors shaping microbial composition, with particular focus on dysbiosis and the role of the gut estrobolome in estrogen metabolism. The review synthesizes data on microbiome alterations associated with endometriosis, adenomyosis, uterine fibroids, endometrial polyps and hyperplasia, gynecologic malignancies, pelvic inflammatory disease, bacterial vaginosis, infertility, and adverse obstetric outcomes including preterm birth and fetal growth restriction. Methodological approaches used to characterize the reproductive tract microbiota, such as vaginal swabs, endometrial sampling, and fecal analysis, are critically discussed, alongside limitations related to low-biomass environments and contamination risk. Evidence regarding therapeutic modulation of the microbiome, including antibiotics, probiotics, hormonal therapies, and emerging microbiota-based interventions, is summarized, as are the effects of gynecologic surgery on microbial translocation and long-term microbial balance. Overall, the available literature supports an association between microbiota alterations and multiple reproductive conditions, although causality remains incompletely defined. Further standardized and longitudinal studies are needed to clarify mechanisms and guide microbiome-informed diagnostic and therapeutic strategies.

Keywords: microbiome; reproductive tract microbiota; vaginal microbiota; endometrial microbiota; gut-uterus axis; estrobolome; dysbiosis; gynecologic diseases; infertility; obstetric outcomes

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1. Introduction

The human *microbiome* encompasses all microorganisms inhabiting the body and their genetic material, while the term *microbiota* refers specifically to these microbial communities within a defined environment [1]. These organisms colonize nearly all mucosal surfaces and play essential roles in homeostasis, immunity, and metabolic balance [2]. Although the gastrointestinal tract hosts the richest and most diverse microbial population, sequencing technologies have revealed distinct microbial ecosystems throughout the female reproductive tract, including vagina, cervix, endometrium, fallopian tubes, ovaries and even the peritoneal cavity, each with unique compositions and functions [3,4].

The gut microbiota, dominated by *Firmicutes, Bacteroidetes, Actinobacteria,* and *Proteobacteria*, contributes to digestion, vitamin synthesis, immune modulation, and protection against pathogens [1,5]. Its equilibrium is crucial for maintaining intestinal barrier integrity and systemic immune tolerance; distruption of this balance, known as **dysbiosis**, is associated with inflammatory and metabolic diseases (inflammatory bowel disease, obesity, metabolic syndrome…), as well as reproductive disorders [3,6].

In contrast, the vaginal microbiota of healthy women is typically dominated by *Lactobacillus* species [7] (*L. crispatus, L. jensenii, and L. iners*), which maintain a protective low pH environment through lactic acid production [4]. Its composition is dynamic and influenced by hormonal fluctuations, sexual activity, hygiene, and other environmental factors. Increased microbial diversity, particularly due to anaerobic or facultative anaerobic species, has been linked to impaired vaginal health. Taxa such as *Chlamydia trachomatis*, *Gardnerella vaginalis*, *Prevotella* species (spp.), *Sneathia* spp., *Bacteroides* spp., *Mobiluncus* spp., and *Atopobium vaginae*, are frequently associated with dysbiosis and adverse gynecological outcomes [2,8], including bacterial vaginosis, pelvic inflammatory disease (PID), cancer, infertility, and endometriosis and obstetric complications [3].

Advances in next-generation sequencing (NGS) have challenged the belief that the upper genital tract is sterile. A low-biomass but distinct microbiota is now recognized in the uterus, fallopian tubes, and ovaries, forming a continuum with the lower tract [9]. This upper-tract microbiota, more diverse than the vaginal one, includes *Lactobacillus, Pseudomonas, Propionibacterium, Acinetobacter, and Streptococcus* [2]. Although not fully understood, it may influence immune regulation, tubal motility, follicular development, fertility and the pathogenesis of inflammatory gynecological diseases.

The endometrial microbiota, though low in density, appears clinically relevant. Predominant genera include *Lactobacillus, Bifidobacterium, and Streptococcus,* with potential role in implantation, pregnancy maintenance, and susceptibility to endometrial pathologies. Similarly, the cervical microbiota acts as an ecological and immunological interface between vaginal and uterus, shaping infection risk and cervical carcinogenesis [3,4].

The peritoneal cavity, once considered sterile, may also harbor microbial DNA and viable bacteria, potentially originating from the reproductive tract or intestinal translocation. These microorganisms may participate in inflammatory processes underlying conditions such as endometriosis or PID [4,6].

Overall, interactions between site-specific microbial ecosystems and host immune-endocrine networks are fundamental to women's reproductive health. Dysbiosis at any anatomical site can alter immunity, hormonal signaling, and tissue homeostasis, contributing to obstetric and gynecological disorders. Understanding the composition and dynamics of the microbiota across the gastrointestinal and reproductive tracts is therefore essential for advancing diagnostic and microbiota-targeted therapeutic strategies [10].

2. Materials and Methods

This narrative review provides an updated synthesis of current evidence on the relationship between the microbiota, its dysbiosis and major gynecological and obstetric diseases.

A structured literature search was conducted in PubMed/MEDLINE and Google Scholar databases for studies published between January 2010 and September 2025, using the terms *"microbiota"*, *"microbiome"*, *"gut microbiota"*, *"vaginal microbiota"*, *"endometrial microbiota"*, *"reproductive microbiota"* and *"dysbiosis"*. Eligible studies included original research, systematic reviews, meta-analyses, and clinical studies written in English and investigating the composition or alterations of the intestinal, vaginal, cervical, endometrial or peritoneal microbiota in women. Animal studies or works lacking microbiological or molecular data were excluded. Titles and abstracts were independently screened by three reviewers (G.S, G.C, and E.P.), and full-text articles meeting inclusion criteria were evaluated for methodological quality and relevance. Data were summarized narratively, with particular attention to mechanisms linking dysbiosis to inflammation, hormonal imbalance, and reproductive dysfunction.

As a narrative review, no formal quality scoring (e.g., PRISMA) or quantitative synthesis was performed; however, heterogeneity in study design, populations and microbiota assessment methods was considered during data interpretation.

3. Etiopathogenesis of the Normal vs. Altered Microbiota

The composition of a healthy microbiome reflects a dynamic balance shaped by intrinsic (age, genetics, ethnicity, immune reactivity and hormonal milieu) and extrinsic factors (diet, physical activity, stress, smoking, sexual behavior, hygiene habits, and exposure to endocrine-disrupting chemicals), all of which influence microbial diversity and function along the gut-reproductive axis [11-12]. These determinants regulate the equilibrium between protective taxa, such as *Lactobacillus* spp. in the reproductive tract and short-chain fatty acid (SCFA), producing bacteria in the gut, and potentially pathogenic organisms capable of promoting inflammation or epithelial dysfunction [13].

Microbial colonization remains highly dynamic: longitudinal studies show that individual profiles fluctuate with physiological transitions, lifestyle changes, pregnancy or medical interventions [14]. Antibiotics, hormonal therapies, chemotherapy and surgical procedures can significantly reshape microbial ecosystems, sometimes resulting in persistent dysbiosis [15-16]. Birth-related factors are also crucial: vaginal birth exposes newborns to maternal vaginal and intestinal flora, rich in *Lactobacillus* and *Bifidobacterium*, whereas cesarean-section favors early colonization by skin-associated taxa such as *Staphylococcus* and *Corynebacterium*, with downstream effects on immune and metabolic development [17].

Diet represents one of the strongest modulators of the microbiome. Fiber-rich diets enhance diversity, SCFA production, gut barrier integrity and immune tolerance, while low-fibers or high-sugar diets reduce microbial resilience and promote pro-inflammatory taxa [5]. When intrinsic and extrinsic stressors exceed host adaptive capacity, the system may shift toward a low-diversity, dysbiotic state characterized by anaerobic or opportunistic overgrowth, epithelial barrier disruption and increased susceptibility to inflammation and infection.

Among nutritional factors, vitamin D plays a key role in microbiome homeostasis. Vitamin D receptors (VDRs), expressed in the gut, immune system, liver, and uterus [18] regulate over 1000 genes involved in microbial homeostasis, gut barrier integrity, immune modulation and pathogen defense [19]. Adequate vitamin D levels supports gut microbiota diversity, promoting beneficial taxa such as *Bacteroidetes*, *Verrucomicrobia*, and *Actinobacteria*, including *Akkermansia muciniphila*, essential for mucosal homeostasis and immune tolerance [20]. Conversely, vitamin D deficiency is linked to a reduced *A. muciniphila*, increased *Firmicutes*, greater gut permeability and systemic inflammation, contributing to dysbiosis [21]. Vitamin D/VDR signaling also suppresses bacteria-induced NF-κB activation and pro-inflammatory cytokine (TNF-α, IL-1β, IL-6) [22-23], while supplementation boosts anti-inflammatory mediators (IL-4, IL-10) and restores microbiota balance [22]. Overall, vitamin D emerges as a key regulator of both gut and reproductive tract microbiota, with implications for immune homeostasis and gynecological health [22,24].

4. Methods for Investigating the Female Genital and Gut Microbiota

Investigating the vaginal and endometrial microbiome requires highly standardized sampling and analytical procedures, as the low biomass of the endometrium and the risk of cervicovaginal contamination necessitate carefully controlled methodologies [4,25]. Endometrial microbial composition can vary with inflammatory states, hormonal fluctuations or pregnancy and sampling must therefore account for potential contamination during cervical passage. For vaginal microbiota assessment, self-collected swabs offer a reliable, convenient and cost-effective option; Forney et al. found no significant differences between self- and clinician-collected vaginal samples [26].

Early endometrial sampling relied on aspirated endometrial fluid obtained via catheters or Pipelle devices, but current evidence supports the superiority of endometrial biopsy in capturing broader microbial diversity [27]. To minimize contamination during transcervical passage, investigators such as Liu et al. (2018) used a Cornier Pipelle with an external protective sheath [28]. Standardization of sampling time is essential due to cyclical microbial variability along the menstrual cycle [29]; the mid-follicular phase is preferred to minimize hormonal confounders [30], while recent antibiotic use or active bleeding warrant exclusion [31].

Over the past 15 years, microbiome characterization has evolved from subjective microscopic evaluation to molecular techniques such as quantitative PCR for targeted pathogens and, increasingly, NGS [35]. NGS of the 16S rRNA gene enables direct analysis of sample DNA and has led to the classification of vaginal microbiota into *community state types* (CSTs): CST I (*L. crispatus* dominance), CST II (*L. gasseri* dominance), CST III (*L. iners* dominance), CST IV (heterogeneous communities with low *Lactobacillus* and high *anaerobes*), and CST V (*L. jensenii* dominance). While *Lactobacillus*-dominated CSTs reflects a protective state, CST IV is associated with bacterial vaginosis and increased susceptibility of sexually transmitted infections (STIs) [32]. For species-level resolution and functional profiling, shotgun metagenomics is increasingly prioritized [33].

Despite advances, heterogeneity in 16S rRNA variable-region primers remains a limitation, contributing to inter-study inconsistencies. A future goal is the establishment of standardized protocols for sampling, sequencing and analysis [28]. Across platforms, best practices include immediate preservation of samples (e.g., at –80 °C), host DNA depletion, and optimized microbial lysis to ensure accurate representation of low-biomass genital microbiota [31].

5. Microbiome and Gynecological Disorders

5.1. Microbiota, Endometriosis and Adenomyosis

Endometriosis and adenomyosis are chronic estrogen-dependent disorders marked by ectopic or infiltrating endometrial-like tissue, persistent inflammation, hormonal imbalance and immune dysregulation. Growing evidence indicates that microbial dysbiosis may modulate these processes and contribute to disease onset and progression [34].

5.1.1. Microbiota and Endometriosis

Women with endometriosis typically show reduced protective *Lactobacillus* spp. in the vaginal microbiota and increased opportunistic taxa such as *Gardnerella vaginalis*, *Atopobium vaginae* and *Ureaplasma* spp. [35]. Endometrial samples reveal a shift toward pro-inflammatory communities, with increased *Fusobacterium*, *Streptococcus*, *Enterococcus*, *Escherichia coli* and *Prevotella* and decreased *Lactobacillus* spp. [36].

Gut dysbiosis, presents in endometriosis, can impair the intestinal barrier, leading to increased permeability (“leaky gut”) and translocation of bacterial products such as lipopolysaccharides (LPS) into the circulation, triggering systemic and pelvic inflammation [37].

The estrobolome also plays a role: β-glucuronidase-producing bacteria (*E. coli, Bacteroides fragilis, Streptococcus agalactiae*) increase estrogen deconjugation and reabsorption, raising circulating estrogen levels and sustaining endometrial tissue proliferation and ectopic lesion growth [38].

The bacterial contamination theory further links dysbiosis to endometriosis: retrograde menstruation may introduce endotoxin-rich (such as LPS) endometrial cells into the peritoneal cavity, especially when vaginal or gut dysbiosis increases Gram-negative bacteria. This activates TLR4 signaling, NF-κB and COX-2 pathways, stimulating angiogenesis, fibrosis and survival of lesions [35,38, 39]. Peritoneal fluid from affected women shows enrichment of *Prevotella*, *Atopobium*, *Veillonellaceae* and *Comamonas*, suggesting ascending or translocated bacteria participate in pathogenesis [40].

5.1.2. Microbiota and Adenomyosis

Although data are more limited, adenomyosis also shows altered reproductive-tract microbiota, with decreased *Lactobacillus* dominance and increased *Gardnerella* and *Prevotella* spp. in uterus and cervix, as well as greater vaginal richness and shifts involving taxa such as *Oscillospirales* and *Ruminococcaceae* [41]. These changes may disrupt the local myometrial immune environment, promoting cytokine release, tissue remodeling and endometrial glandular infiltration. Estrobolome-related estrogen reactivation observed in endometriosis may similarly contribute to the hyperestrogenic milieu of adenomyosis [34].

Given shared features (chronic inflammation, immune activation, estrogen dependence, tissue invasion) and overlapping dysbiosis patterns, endometriosis and adenomyosis may involve common microbiota-mediated inflammatory mechanisms.

Collectively, dysbiosis may trigger a cascade involving immune activation, increased gut permeability, endotoxin translocation, altered estrogen metabolism and direct microbial contamination of the peritoneal cavity, sustaining chronic inflammation and hormonal imbalance [42].

Although causality is unconfirmed and human data remain heterogeneous, microbiome-targeted strategies (probiotics, prebiotics or dietary interventions), are emerging as promising adjuncts for estrogen-driven gynecological diseases [41-42].

5.2. Microbiota and Fibromatosis

Recent evidence supports a gut-uterus axis in the onset and progression of uterine fibroids (UFs), with dysbiosis emerging as a contributor to hormonal, metabolic and inflammatory alterations that favor fibroid growth [43]. Women with UFs often show reduced gut microbial diversity, enrichment of pro-inflammatory or estrogen-modulating taxa such as *Bacteroides*, *Prevotella*, *Ruminococcus*, and β-glucuronidase-producing *Enterobacteriaceae* [44-45] as well as reduced production of SCFAs, key regulators of immune balance and smooth-muscle proliferation [44-45]. These changes promote enhanced estrogen recycling via the estrobolome, contributing to the hyperestrogenic milieu typical of fibroid development [46].

At the genital-tract level, fibroid patients display increased anaerobic species linked to inflammation and extracellular matrix accumulation, including *Gardnerella vaginalis*, *Atopobium vaginae*, *Sneathia sanguinegens*, and *Prevotella bivia*, alongside reduced *L. crispatus* and *L. jensenii* [47]. Such alterations may influence fibroid biology through toll-like receptor (TLR) activation, oxidative stress and dysregulated cytokines (IL-6, TNF-α and TGF-β), all implicated in leiomyoma pathophysiology [48].

Interestingly, fibroid tissue itself may harbor distinct microbial DNA signatures. Higher prevalence of *Acinetobacter*, *Pseudomonas*, *Streptococcus*, and *Cutibacterium acnes* have been identified within leiomyomas compared with adjacent myometrium, suggesting a local microbial niche that may affect tumor behavior [48].

Microbiota composition may also modulate treatment response. For example, vitamin D supplementation appears more effective in restoring endometrial immune balance when supported by a favorable gut microbial profile, indicating a potential synergy between microbiome-targeted strategies and medical therapy [24].

Overall, emerging data depict uterine fibroids not solely as hormone-dependent lesions but as a condition embedded within a broader microbial–immune–endocrine network, in which gut and genital microbiota may influence susceptibility, progression, and therapeutic outcomes [47].

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5.3. Microbiota and Endometrial Polyps

Growing evidence indicates that women with endometrial polyps (EPs) exhibit distinct alterations in both vaginal and intrauterine microbiota. These changes consistently reflect a shift away from Lactobacillus dominance toward an over-representation of pro-inflammatory or potentially pathogenic taxa.

Tian et al. reported **significantly reduced vaginal Lactobacillus spp.**, particularly *L. crispatus*, in women with endometrial polypoid lesions, accompanied by enrichment of **Gardnerella**, **Prevotella**, **Atopobium** and **Sneathia**, a pattern resembling bacterial vaginosis–like dysbiosis and associated with local inflammation [49]. Similarly, Zhao et al., using 16S rRNA sequencing of endometrial samples, reported a **higher microbial diversity** and increased **Proteobacteria**, **Bacteroidetes**, *Escherichia/Shigella*, *Streptococcus*, and *Enterococcus* in EP patients, suggesting that a dysbiosis may contribute to epithelial proliferation and immune dysregulation [50].

Vanakova et al. further confirmed that the intrauterine microbiota in EPs is characterized by reduced Lactobacillus prevalence and increased **opportunistic genera such as *Gardnerella, Prevotella*, and *Peptoniphilus*** [51], changes linked to heightened inflammatory signaling and impaired mucosal immunity.

Collectively, these findings support a reproducible dysbiosis **pattern** in EPs, marked by lower Lactobacillus and higher abundance of anaerobic and facultative anaerobic bacteria. Whether dysbiosis is a cause, consequence, or co-factor in polyp development remains unclear, but these microbiome signatures may hold diagnostic or therapeutic relevance [49].

5.4. Microbiota, Sexually Transmitted Infections and Pelvic Inflammatory Disease

Epidemiological studies consistently show that a Lactobacillus-dominated vaginal ecosystem protects against STIs. Tamarelle et al. meta-analysis demonstrated that high-Lactobacillus communities significantly reduce the risk of human papillomavirus (HPV) and Chlamydia trachomatis aquisition [52], while laboratory work by Nardini et al. showed that L. crispatus supernatants rich in lactic acid directly inhibit C. trachomatis infectivity in vitro [53]. In essence, a low-diversity, lactobacilli-rich microbiome reinforces the epithelial barrier and creates an hostile environment to pathogens.

Vaginal dysbiosis, especially bacterial vaginosis (BV), has the opposite effect and is a well-established risk factor for multiple STIs. Women with BV exhibit markedly higher rates of Chlamydia, Neisseria gonorrhoeae, HIV, and other infections, as summarized by Brotman [54]. Molecular studies confirm this trend: STI positive women show severe depletion of L. crispatus and increased anaerobes such as Gardnerella, Prevotella and other BV-associated taxa [55-56]. These anaerobes secrete enzymes (e.g., sialidases, proteases) and SCFA that damage cervical mucus and epithelium, promote inflammation and increase vaginal pH, all of which facilitate pathogen establishment [55,57].

Behavioral factors further amplify risk. High-risk population, including sex workers, display more diverse, Lactobacillus-poor vaginal microbiota and higher STI rates. Wessels et al. reported significantly reduced Lactobacillus and increased bacterial diversity in sex workers compared with controls [58]. Likewise, Mehta et al. (2023) found that adolescents who later contracted STIs had much lower L. crispatus levels than those who remained STI-negative [59]. Overall, these data confirm that a Lactobacillus-rich microbiota is protective, whereas dysbiosis greatly increases susceptibility to STIs [52].

The same principles apply to PID. A stable Lactobacillus-dominated vaginal microbiota maintains mucus integrity and limits inflammation in the upper genital tract, whereas dysbiosis promotes proliferation of BV-associated bacteria whose enzymes degrade the cervical barrier and facilitate microbial ascent into the uterus and fallopian tubes [55,57].

5.5. Microbiota and Vaginosis

BV occurs when the normal Lactobacillus-dominated flora is replaced by a diverse anaerobe-rich community. This transition involves a marked depletion of Lactobacilli and overgrowth of facultative and strict anaerobes such as *Gardnerella vaginalis, Atopobium vaginae, Prevotella* species, *Mobiluncus* species, *Sneathia/Leptotrichia, Peptostreptococcus and Mycoplasm*a [60]. The shift toward a high-diversity microbiota increases vaginal pH (typically >4.5) due to reduced lactic acid production. BV has no single causative pathogen; it presents a vaginal ecosystem imbalance in which different women may harbor different dominant bacteria, and multiple taxa can collectively produce the syndrome [60]. What we call "BV" is a common clinical outcome (vaginal dysbiosis) that can be provoked by various bacterial community structures along with host factors.

Culture-independent studies have identified additional BV-associated organisms, including *BVAB1–3 (BV-associated bacteria 1–3)*, underscoring the polymicrobial nature of BV and the broader microbial diversity seen in dysbiosis compared with the *lactobacilli*-rich healthy state [61].

A hallmark of BV dysbiosis is the formation of a polymicrobial biofilm on the vaginal epithelium. *G. vaginalis* plays a central role by adhering to epithelial cells and co-aggregating with other BV-associated species, such as *Atopobium vaginae* [62]. Within this biofilm, microbes are embedded in an extracellular matrix that protects them from antibiotics and immune clearance, enabling regrowth and relapse. Clinically, post-treatment recurrence is common: over 50% of women experience BV again within 12 months of antibiotic therapy [63].

Relapse is often linked to residual BV-associated bacteria that persist despite treatment. Women who recur tend to have higher post-treatment abundance of organisms such as *A. vaginae*, *Gardnerella* or *Aerococcus* than women who achieve long-term remission [64]. In some refractory cases, core BV bacteria show minimal reduction even immediately after therapy, suggesting antibiotic tolerance within biofilms. Computational modeling further indicates that specific pre-treatment community states may predispose to persistence or recurrence [65]. Together, these findings highlight biofilm resilience as a major driver of BV chronicity.

A fundamental limitation of antibiotics is that they reduce pathogen load but do not promote restoration of *Lactobacillus* species needed to re-establish a stable microbiome. After treatment, the vaginal niche may remain insufficiently colonized by lactobacilli, allowing BV-associated bacteria to rebound, especially if protected in biofilms or reintroduced by partners. This has stimulated growing interest in adjunctive microbiome-directed therapies [66]. One promising strategy is Lactobacilli-based, administered orally or intravaginally, to recolonize the vagina with beneficial microbes. A randomized placebo-controlled trial by Cohen et al. 2020 tested intravaginal *L. crispatus* (LACTIN-V) for 11 weeks following metronidazole treatment and showed a significantly lower BV recurrence rate by 12 weeks (30% vs. 45% in the placebo group), corresponding to a 34% relative reduction, accompanied by successful colonization of the administered strain [67].

5.6. Microbiota and Cancer

5.6.1. Microbial Dysbiosis and Oncobiosis

Advances in 16S rRNA sequencing show that dysbiosis is a consistent feature of gynecological malignancies; when associated with neoplasia, this shift is termed "*oncobiosis*" and may represent a modifiable risk factor [68]. A systematic review of 21 studies identified reproducible dysbiotic patterns across all gynecological cancers, with microbiota composition correlating with disease grade and histological subtype [3].

5.6.2. Endometrial Cancer

Endometrial cancer (EC) exhibits a characteristic dysbiotic signature defined by *Atopobium vaginae* and *Porphyromonas somerae* simultaneously, particularly with elevated vaginal pH, demonstrating 73–93% sensitivity and 67–90% specificity [69]. Meta-transcriptomic analyses identified over 5500 active bacterial species in EC with pathway enrichment supporting epithelial-mesenchymal transition and tumor migration [70]. Despite heterogeneity in microbial richness, endometrial cancer consistently displays distinct microbiome profiles compared with controls, supporting the presence of stable, disease-associated microbial signatures [3].

Vaginal CST profiling shows grade-dependent clustering: benign disease with *L. crispatus*, low-grade EC with *L. iners* and high-grade EC with diverse *anaerobes* [71]. *Fusobacterium ulcerans* and *Prevotella bivia* are enriched sixfold in high-grade tumors [71]. Mechanistic studies demonstrate that *Anaerococcus vaginalis* induces reactive oxygen species production in endometrial fibroblasts, evidencing inflammation-mediated carcinogenesis [72]; while fungal dysbiosis, particularly *Penicillium,* may promote estradiol-like metabolite production, suggesting fungal hormone mimicry [73].

Dysbiosis also fuels inflammation via TLR2/TLR4 activation and lipopolysaccharides (IL-6/IL-8/TNF-α) production [73]. Altered bacterial β-glucuronidase activity increases estrogen systemic levels [3]. *P. somerae* invades endometrial cells and produces succinate, stabilizing HIF-1 and promoting angiogenesis [3]. Recent TCGA-based analysis identified 26 taxa linked to prognosis, with low-risk profiles showing enhanced immunotherapy responsiveness [3].

5.6.3. Ovarian Cancer

Ovarian cancer exhibits compartment-specific dysbiosis. Vaginal microbiota in ovarian cancer, especially, especially BRCA1/2 carriers, show marked *Lactobacillus* depletion with non-Lactobacillus-dominant communities predominating [74]. Upper genital tract samples are enriched in *Acinetobacter, Sphingomonas and Methylobacterium*, with reduced diversity compared to normal fallopian tube tissue [75]. The peritoneal microbiome exhibits decreased diversity and increased gram-negative colonization that may facilitate metastatic spread [76].

Lysophosphatidic acid accumulation in ascites, derived from gram-negative lysophospholipids, further promotes proliferation and invasion [74]. Sexual transmission of *Chlamydia trachomatis* increases ovarian cancer risk by 90-fold in high-antibody-titer women, establishing infection-dysbiosis synergy in ovarian carcinogenesis [74].

5.6.4. Cervical Cancer

Altough HPV is the primary driver in cervical cancer, vaginal dysbiosis strongly influences HPV acquisition, persistence, and malignant progression [68]. *Lactobacillus* depletion and enrichment of BV-associated taxa (*Gardnerella vaginalis, anaerobes*) increase HPV transmission risk and delay viral clearance [68]. Dysbiotic microbiota promote cervical inflammation via TLR signaling and cytokine (IL-6/IL-8) production, creating a permissive microenvironment. By contrast, *Lactobacillus* species support local IgA production, epithelial integrity and regulatory T-cell activity, providing protection against HPV-mediated neoplasia [74].

Dysbiosis is a unifying hallmark across gynecological cancers, with distinct microbial signatures linked to cancer type, grade, and treatment responsiveness. Because the microbiome is modifiable, it holds promise for biomarker development and targeted interventions, probiotics, diet-based strategies and selective antimicrobials. Large prospective studies are needed to establish causality and translate these findings into clinical practice.

5.7. Microbiota and Infertility

Infertility affects up to 15% of couples worldwide and a substantial proportion of cases remain idiopathic despite advances in assisted reproductive technologies (ART). Increasing evidence suggests that genital tract microbiota alterations may contribute to infertility by disrupting local immune homeostasis, impairing gamete function and compromising embryo implantation [77-78].

In healthy women, the vaginal microbiota is dominated by *Lactobacillus* species (*L. crispatus*, *L. jensenii*, *L. gasseri*), which maintain a low pH and protect against pathogens [79]. Vaginal dysbiosis, characterized by reduced *Lactobacillus* abundance and enrichment of *Gardnerella vaginalis*, *Atopobium vaginae*, or *Prevotella* spp. has been linked to lower implantation and pregnancy rates, especially in in vitro fertilization (IVF) settings [77, 80]. Elevated levels of Gram-negative lipopolysaccharide endotoxin have been detected in menstrual effluents of women with implantation failure, supporting a link between bacterial components and local inflammatory activation [80]. The uterine cavity, once considered sterile, is now recognized as a low-biomass microbial environment continuous with the lower genital tract [4]. NGS has identified microbial communities in the endometrium and follicular fluid, suggesting potential communication between reproductive compartments [81]. A *Lactobacillus*-dominant endometrial microbiota correlates with higher implantation and live-birth rates, whereas increased diversity or the presence of taxa such as *Streptococcus*, *Prevotella* or *Gardnerella* is associated with poorer IVF outcomes, likely through inflammatory signaling and impaired endometrial [81-82].

Emerging data also highlights the role of the male genital microbiota in fertility. The seminal microbiome is not sterile, harbors a diverse microbiota, and enrichment of genera such as *Prevotella*, *Finegoldia*, and *Campylobacter* spp. has been linked with reduced sperm motility, abnormal morphology, and DNA fragmentation, potentially via inflammatory pathways or direct microbial toxicity [83]- Moreover, microbial exchange between sexual partners may reduce vaginal *Lactobacillus* dominance, contributing to unexplained infertility [84]. Metagenomic analyses of infertile couples undergoing ART reveal sex-specific microbial signatures and significant microbial overlap between partners [80]. While female samples are typically *Lactobacillus*- dominated, male genital microbiota displays higher diversity and include BV-associated-taxa [81-82]. In a pivotal study, Baud et al. (2019) demonstrated that male genital samples often harbor *Prevotella*, *Finegoldia*, *Porphyromonas*, and *Mobiluncus*, BV-associated, suggesting that the male partner may act as a microbial reservoir influencing the vaginal microbiota, with a possible cross-contamination, and female reproductive outcomes, supporting the hypothesis of bidirectional microbial transmission [85].

Therapeutic manipulation of the reproductive microbiota remains experimental. Empirical antibiotic use before IVF has shown inconsistent benefits, and probiotic supplementation, including intravaginal *Lactobacillus* administration, has produced inconclusive results [86-87]. Therefore, personalized approaches based on microbiome profiling may represent a promising strategy to improve ART outcomes and address idiopathic infertility [87], although robust longitudinal studies are needed to established causality and guide targeted interventions.

5.8. Microbiota and Obstetric Complications

The maternal microbiota plays a pivotal role in pregnancy, influencing maternal health, fetal development and neonatal microbial colonization. Vaginal, cervical, placental, or intestinal dysbiosis has been increasingly associated with obstetric complications, such as preterm birth, preeclampsia, gestational diabetes mellitus (GDM), and premature rupture of membranes (PROM) [78,88]. During healthy pregnancy, the vaginal microbiota is typically dominated by *Lactobacillus* spp. (*L. crispatus*, *L. jensenii)*, which maintain an acidic environment (pH < 4.5) by producing lactic acid and bacteriocins, limiting pathogen overgrowth. In contrast, reduced *Lactobacillus* abundance with enrichment of anaerobes (*Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella*, and *Ureaplasma*) is strongly correlated with BV and adverse outcomes, particularly spontaneous preterm birth and chorioamnionitis [89].

Beyond the lower genital tract, emerging evidence suggests that the intrauterine environment may harbor low-biomass microbial communities capable of influencing pregnancy outcomes [90]. Although the existence of a distinct placental microbiome remains debated, dysbiotic microbial signals, arising from ascending infection or hematogenous spread from the oral cavity or gut, may contribute to sterile intrauterine inflammation, leading to premature labor, fetal growth restriction, or early pregnancy loss [89–91]. In particular, women with recurrent miscarriage often display reduced *Lactobacillus* dominance and increased colonization by *Gardnerella*, *Atopobium*, and *Streptococcus* spp., implicating altered vaginal and endometrial microbiota in impaired implantation and early placentation [91].

Maternal dysbiosis composition also shapes neonatal health. Delivery mode critically influences early microbial colonization: vaginally delivered neonates acquire microbiota rich in *Lactobacillus*, *Bacteroides* and *Bifidobacterium*, whereas elective cesarean section is associated with delayed microbial maturation and predominance of skin- and environment-associated taxa such as *Staphylococcus* and *Corynebacterium* [92]. Cesarean delivery after labor onset, particularly at full cervical dilation, appears to partially restore microbial exposure, resulting in a neonatal microbiota composition closer to those observed after vaginal birth and potentially more favorable for immune development [5, 93].

Overall, these data underscore the importance of maintaining maternal microbiota homeostasis throughout pregnancy and delivery, as dysbiosis may affect obstetric outcomes, neonatal microbial imprinting and early immune programming.

6. Uterine-Gut Microbiota Axis and Its Implications for Gynecological Health

Growing evidence supports a bidirectional interaction between the intestinal and uterine microbiota, commonly referred to as the *gut–uterus axis* [4,9]. Through its effects on systemic immunity, metabolism and estrogen homeostasis, the gut microbiota can influence endometrial microbial composition and immune tone. In dysbiotic states, increased intestinal permeability (“leaky gut”) facilitates the translocation of bacterial metabolites and endotoxins, such as LPS, into the bloodstream, promoting chronic low-grade inflammation and immune activation [6]. These processes may disrupt endometrial receptivity, alter hormonal signaling and contribute to inflammatory gynecological conditions, including endometriosis, chronic endometritis, polycystic ovary syndrome (PCOS) [6, 11, 34].

Microbial and immunological crosstalk between the gut and female genital tract further suggests that intestinal dysbiosis can predispose to vaginal and uterine microbial imbalance [24]. Gut microbial shifts characterized by reduced *Lactobacillus* and *Bifidobacterium* and enrichment of *Proteobacteria* and *Firmicutes*, increase β-glucuronidase activity, enhancing estrogen deconjugation and reabsorption and thereby sustaining estrogen-dependent diseases such as endometriosis and adenomyosis [38].

Clinically, a strong overlap between intestinal and gynecological diseases supports this axis. Up to 60–70% of women with endometriosis report irritable bowel syndrome (IBS)-like symptoms, while patients with inflammatory bowel disease (IBD) have approximately a twofold increased risk of endometriosis or chronic pelvic pain [94]. Conversely, endometriosis is associated with higher prevalence of gastrointestinal disorders, including IBS (odds ratio 2.5–3.0) and functional constipation or diarrhea, indicating shared pathogenic mechanisms involving gut barrier dysfunction, dysbiosis and systemic inflammation [95].

Overall, the gut-reproductive microbiota axis interplay represents a key regulato of women’s health, whereby intestinal homeostasis supports uterine microbial balance and reproductive function, while dysbiosis and increased gut permeability may propagate inflammatory signals that affecting the reproductive tract.

7. Therapeutic Modulation of the Gut-Reproductive Microbiota

The intestinal and genital microbiota are highly dynamic ecosystems that can be substantially influenced by pharmacological interventions. Antibiotics are among the strongest disruptors of gut-vaginal microbial homeostasis: even short courses of broad-spectrum antibiotic reduce microbial diversity, deplete commensal *Lactobacillus* and *Bifidobacterium* spp. and favor opportunistic colonization (*Gardnerella vaginalis*, *Candida albicans* or *Clostridium difficile)* [16, 86]- In the female genital tract, these changes increase susceptibility to BV, recurrent vulvovaginal candidiasis and post-antibiotic dysbiosis [16]. Similarly, hormonal therapies, including oral contraceptives and hormone replacement therapy, also modulate estrogen-dependent microbial communities by altering vaginal pH and glycogen availability [16, 29]. Estrogen promotes glycogen deposition in the vaginal epithelium, promoting *Lactobacillus* dominance and lactic acid production, whereas hypoestrogenic states, physiological (menopause) or iatrogenic (GnRH analogues), are associated with reduced *Lactobacillus*, elevated vaginal pH and increased anaerobic or pathogenic taxa [96]. Long-term hormonal contraceptive use may influence gut microbiota composition, bile acid metabolism and systemic inflammation. In men, antibiotic exposure or androgen-suppressive therapies can similarly induce seminal microbiota, potentially affecting fertility [97].

Interest has therefore shifted toward strategies aimed at microbiota modulation rather than eradication Probiotics, live microorganisms, have shown benefit in restoring vaginal eubiosis, particularly Lactobacillus-dominated communities protective against infections and inflammation [98]. Prebiotics, nondigestible substrates, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), selectively stimulate beneficial gut bacteria and indirectly support genital tract homeostasis through immune modulation, especially after antibiotic or hormonal disruption [12]. Postbiotics, bioactive compounds derived from microbial metabolism, such as SCFA and cell wall components, are emerging as safer alternatives in immunocompromised patients or during pregnancy, exerting anti-inflammatory and barrier-enhancing effects and potentially improving endometrial receptivity via the gut–reproductive axis.[12,99]. Combined or sequential approaches (prebiotic plus probiotic or probiotic plus postbiotic) may be particularly effective by providing both metabolic substrates and functional modulation. Next-generation probiotics, such as *Lactobacillus crispatus* CTV-05 or *L. rhamnosus* GR-1 and *L. reuteri* RC-14, administered orally or intravaginally, have demonstrated efficacy in preventing BV recurrence and improving vaginal microbiota composition, especially in women with recurrent dysbiosis or implantation failure [100]. Notably, intravaginal *L. crispatus* CTV-05 (LACTIN-V) following antibiotic treatment significantly reduces BV recurrence and promotes long-term protective *L. crispatus* dominance [67].

Finally, fecal microbiota transplantation (FMT), although still experimental in gynecological settings, has shown potential in restoring intestinal eubiosis in women with severe dysbiosis and recurrent genital infections [101]. Overall, microbiota modulation emerges as a promising preventive and adjunctive strategy in gynecological and obstetric care. Future research will likely focus on personalized microbiome-based interventions, integrating genomic, metabolomic, and hormonal profiling to optimize reproductive outcomes and long-term microbial resilience [102].

8. Microbiota and Gynecologic Surgery

Gynecologic surgeries, including hysterectomy, myomectomy, operative hysteroscopy or surgical curettage, induce significant disturbance in both genital and intestinal microbial communities. Instrumentation of the cervico-vaginal canal and uterine cavity may facilitate microbial translocation, allowing taxa typically confined to the lower genital tract (*Gardnerella*, *Prevotella*, *Atopobium*, *Streptococcus*, *Enterococcus*, *Escherichia*, *Shigella*) to access deeper tissues or the bloodstream, transiently amplifying inflammation. Perioperative factors including antibiotic prophylaxis, surgical stress, bowel preparation, and anesthesia further reduce microbial diversity and favor opportunistic colonization [103].

Postoperative microbial shifts are also influenced by endocrine alterations. A case-control study in women undergoing transabdominal hysterectomy for uterine fibroids showed increased postoperative follicle-stimulating hormone (FSH) levels, alongside reduced estradiol (E2) and anti-Müllerian hormone (AMH), indicating altered ovarian function despite ovarian preservation [104]. These hormonal changes were associated with gut dysbiosis, characterized by increased *Proteobacteria* and *Firmicutes* and reduced *Bacteroidetes* [103, 104].

Post-hysterectomy cohort-studies further demonstrate that surgery induces long-term gut microbiota remodeling, including partial recovery of SCFA-producing taxa and a reduction in pro-inflammatory bacteria, changes associated with lower systemic inflammation and improved metabolic markers [105,106]. Nevertheless, early postoperative phases, especially after hysterectomy with salpingo-oophorectomy, often show a transient imbalance with increased *Escherichia/Shigella* and *Enterococcus* and reduced *Lactobacillus* dominance [107].

Overall, gynecologic surgery produces both acute and long-term alterations of the genital and intestinal microbiota through mechanical disruption, endocrine changes, and perioperative exposures. These shifts may influence postoperative recovery, infection susceptibility, and long-term inflammatory and metabolic homeostasis [43].

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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Appendix A

The appendix is an optional section that can contain details and data supplemental to the main text—for example, explanations of experimental details that would disrupt the flow of the main text but nonetheless remain crucial to understanding and reproducing the research shown; figures of replicates for experiments of which representative data is shown in the main text can be added here if brief, or as Supplementary data. Mathematical proofs of results not central to the paper can be added as an appendix.

Appendix B

All appendix sections must be cited in the main text. In the appendices, Figures, Tables, etc. should be labeled starting with "A"—e.g., Figure A1, Figure A2, etc.

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