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# Alterations in vaginal and urinary microbiota in menopause and associated pathologies: A narrative review

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## Abstract

**Background:** In the premenopausal stage, the vaginal microbiota is characterized by a high abundance of *Lactobacillus*, a key genus for preserving a healthy vaginal environment. However, the estrogen decline associated with menopause modifies this microbial community, leading to a reduction in *Lactobacillus* and promoting the proliferation of anaerobic bacteria, thereby increasing the risk of dysbiosis, as observed in bacterial vaginosis. Likewise, the urinary microbiota undergoes alterations that heighten the susceptibility of postmenopausal women to urinary tract infections. Hormonal changes also cause symptoms such as vaginal dryness, irritation, and dyspareunia, resulting from urogenital atrophy, which affects not only physical health but also emotional well-being and quality of life. **Aim:** The aim of the study was to describe the changes of the vaginal and urinary microbiota's associated with estrogen deficiency in menopause, as well as their relationship with relevant clinical conditions, including pelvic floor diseases, genital infections, periodontal disease, and gynecological cancers. **Relevance for patients:** Understanding these microbial changes is crucial for optimizing clinical management and improving the overall health of women in this stage of life, as these alterations represent an emerging field of research with important diagnostic and therapeutic implications.

***Keywords:*** Vaginal microbiota; Urinary microbiota; Menopause; Associated pathologies

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## 1. Introduction

Menopause marks the end of the female reproductive stage. It is accompanied by a decrease in estrogen levels, which not only affects women's overall health but also alters the composition and diversity of the lower genital tract microbiota.[1] The development of molecular techniques has enabled a deeper understanding of the diversity and complexity of this microbial community.[1,2] In premenopausal women, the vaginal microbiota (VM) is predominantly composed of beneficial bacteria, particularly from the *Lactobacillus* genus, which help prevent infections through the production of hydrogen peroxide and lactic acid, creating a protective acidic environment.[1,3] After menopause, the decline in estrogen levels alters the vaginal microbial community, leading to a decrease in *Lactobacillus* abundance[4,5] and promoting microbial imbalance with an overgrowth of anaerobic bacteria (dysbiosis). This shift increases the risk of infections such as bacterial

vaginosis (BV).[1] Estrogen plays a key role in regulating vaginal pH and stimulates epithelial cells to produce glycogen, an essential nutrient for *Lactobacillus* survival.

The urinary microbiota is also affected by menopause, although its study has been less frequent. Urine in healthy women is generally sterile, but with the decrease in estrogen, the microbiota in the urethra and bladder change, and the pH is altered. Alterations in the urinary microbiota may facilitate colonization by uropathogenic bacteria, increasing the frequency of recurrent urinary tract infections (UTIs/rUTIs) in postmenopausal women.[6,7] In addition, hormonal changes also affect vaginal hydration and mucus production. These symptoms, including vaginal dryness, irritation, and pain during intercourse, result from vaginal atrophy caused by estrogen deficiency.[1,4] Recurrent genitourinary infections and irritation symptoms can negatively impact the emotional well-being of women, which is not always addressed in medical studies. This suggests that the VM contributes not only to protection but also to maintaining vaginal health and the overall quality of sexual function.[1] In this context, menopause has been associated with changes in the composition, diversity, and activity of the microbiota in different body regions—most notably the vaginal, intestinal, and urinary tracts—which may influence the general health of postmenopausal women.[8] The decrease in estrogen levels, along with the alteration of the vaginal and urinary microbiota, may influence a range of health conditions, including urinary incontinence, genital infections, genital discomfort, gynecological cancer, and periodontal disease.[5,8] This set of menopause-related diseases constitutes an emerging field of research that has begun to gain attention in recent years.[8]

This narrative review seeks to examine the alterations in the vaginal and urinary microbiota that occur during menopause and to identify the related conditions that may impact women's systemic health. Gaining insight into the underlying causes of these changes could support more effective strategies for managing these disorders.

## 2. Materials and methods

This review included the following types of publications: systematic reviews, narrative reviews, meta-analyses, and relevant original studies (cohort studies and case–control studies) that demonstrated a low or very low risk of bias and a high or moderate likelihood of establishing a causal relationship between the vaginal and urinary microbiota and disorders associated with menopause. Articles published from 1990 onwards were included, provided they were available in the following databases: PubMed, Elsevier, Science Direct, Wiley, Scopus, Ovid, and SciELO, and were directly and explicitly relevant to the subject of interest. All publications that did not meet the established criteria, as well as studies on the microbiome and conditions unrelated to menopause, were excluded.

## 3. Vaginal and urinary microbiota in fertile women

In healthy, fertile women, estrogen levels and glycogen availability directly influence the VM by promoting the dominance of *Lactobacillus*, thickening of the stratified squamous vaginal epithelium, and increasing cervical mucus secretion.[9,10] *Lactobacillus* species are essential in maintaining the vaginal ecosystem, as they produce lactic acid (which lowers vaginal pH), hydrogen peroxide ($H_2O_2$), and bacteriocins—compounds with antimicrobial, antiviral, and immunomodulatory properties.[9] They also compete for adhesion sites with other bacteria, helping to prevent sexually transmitted infections (STIs) and the overgrowth of endogenous opportunistic microorganisms.[11-14]

Among healthy women of European descent, *Lactobacillus crispatus*, *Lactobacillus gasseri*, and *Lactobacillus jensenii* are the predominant $H_2O_2^-$ and bacteriocin-producing species, while in African American women, *Lactobacillus iners* is most frequently detected.[15] Understanding the prevalence of species that colonize the vaginal ecosystem is useful for the development of products for *Lactobacillus* replacement therapy.[15]

This direct effect of estrogen on the quality and increase of *Lactobacillus* has been demonstrated in reproductive-aged women using contraceptives containing estrogen. According to a review conducted in Australia, contraceptive methods that include estrogen may support a favorable VM in certain groups of women. However, the effects of progestin-only contraceptives on the vaginal environment remain uncertain, and further research is required to clarify their potential role in negative reproductive and sexual health outcomes.[16]

Advances in bacterial gene sequencing, particularly targeting the *16S ribosomal RNA* (*rRNA*) gene, have enhanced our understanding of the diversity of microbial communities in the female genital tract.[2,4,9,15] A study conducted on asymptomatic women of reproductive age in North America, including participants of Asian, White, Black, and Hispanic backgrounds, identified five distinct types of microbial community structures. Four of these were primarily dominated by different *Lactobacillus* species: community state (CST) type I (*L. crispatus*), CST II (*L. gasseri*), CST III (*L. iners*), and CST V (*L. jensenii*). The fifth type, CST IV, consisted of a more diverse group of bacteria, mostly anaerobic species.[15] It was observed that the predominance of lactobacilli in the VM is higher,

and vaginal pH is lower, in White women. In contrast, the predominance of lactobacilli decreases and vaginal pH gradually increases in women of Asian, Hispanic, and Black descent, respectively. In addition, CST III (*L. iners*) is associated with microbial states of high diversity.[15] A bidirectional interaction exists between the female reproductive system and the VM. Physiological changes occurring from birth and extending beyond menopause can impact the VM; while conversely, the VM itself can affect reproductive functions.[9]

## 4. Vaginal and urinary microbiota in menopause

The decline in estrogen levels during menopause leads to a reduced presence of *Lactobacillus* species, decreased glycogen in vaginal epithelial cells, and lower lactic acid production. Consequently, vaginal pH rises, making the environment more prone to infections. This shift in VM increases the risk of conditions such as BV, aerobic vaginitis (AV), and vaginal candidiasis in postmenopausal women. In addition, estrogen deficiency and low glycogen contribute to vaginal atrophy, characterized by thinning of the squamous epithelium (mainly basal and parabasal layers), decreased vaginal secretions, dryness, and painful intercourse.[1,4] Several studies confirm that both the diversity and abundance of lactobacilli diminish after menopause. A study from Sweden comparing fertile and postmenopausal women found a higher frequency of *L. crispatus* colonization in fertile women ($p$=0.0036).[17] Similarly, Zhang *et al.*[18] reported a reduced diversity of *Lactobacillus* spp. in postmenopausal compared to premenopausal women ($p$<0.05). Another investigation demonstrated that premenopausal women had significantly greater free glycogen levels, which correlated with higher *Lactobacillus* counts, while postmenopausal women showed lower glycogen and *Lactobacillus* levels ($p$=0.03).[19] Using *16S rRNA* gene sequencing, it was shown that during menopause, CST IV becomes predominant, marked by diverse bacterial populations and a lack of *Lactobacillus*. CST IV-A contains a few lactobacilli and various anaerobes such as *Anaerococcus*, *Peptoniphilus*, and *Prevotella*. Conversely, CST IV-B is characterized by a large proportion of *Atopobium* along with *Prevotella*, *Parvimonas*, *Sneathia*, *Gardnerella*, *Mobiluncus*, and *Peptoniphilus*.[20] The emergence of CST IV is linked to BV, a microbiota imbalance that causes symptoms like unpleasant odor, discharge, and discomfort.[1,4] BV is more prevalent after menopause and is associated with increased risks of UTIs, STIs, and gynecological problems such as pelvic inflammatory disease (PID). Women who exhibit CST III vaginal profiles during perimenopause tend to shift toward CST IV-A after menopause, which is more closely related to atrophic vaginitis.[21] Although molecular methods to study the microbiome have advanced, most clinical settings worldwide still rely on traditional approaches such as Gram staining and Nugent scoring to evaluate VM.[1] Exogenous sex steroids used in hormone replacement therapy (HRT) for menopause are commonly employed to manage menopausal symptoms. There is growing evidence that estrogen-containing compounds may promote a healthier VM. In the previously mentioned Australian review, it was found that among postmenopausal women using HRT, topically applied exogenous estrogen was associated with an increased prevalence of *Lactobacillus*.[16]

Compared to the VM, information on the urinary microbiota remains limited. Some findings suggest that hormonal imbalances after menopause may lead to dysbiosis, potentially contributing to both anatomical and functional changes that impact women's general health. These alterations can compromise vaginal integrity and contribute to the onset of genitourinary syndrome of menopause (GSM). In addition, an imbalanced urinary microbiota has been linked to symptoms like urinary urgency and incontinence, as well as conditions such as interstitial cystitis, bladder pain syndrome, and neurogenic bladder. As these issues frequently occur in postmenopausal women, the influence of hormonal shifts on microbial composition may be significant. Menopause is associated with increased alpha diversity in the urinary microbiome and a reduced abundance of *Lactobacillus* in urine—variations that may precede rUTIs like cystitis. Further investigation is essential to clarify how menopause-related changes in urinary microbiota affect the development of urinary tract disorders.[22]

## 5. Gut microbiome

The importance of the gut microbiota in overall health and disease is now widely recognized. A recent editorial[23] discusses how the balance or imbalance of the intestinal microbiota affects immunity and general health. Factors such as genetics, diet, age, stress, medications, and mode of delivery determine the microbial composition of the gut and, consequently, its influence on immune responses. A microbiota in eubiosis, or in a balanced state, promotes the production of metabolites with immunoregulatory and protective effects, maintaining the organism's homeostasis and health. In contrast, dysbiosis or microbial imbalance can trigger inflammation and epithelial dysfunction.

The editorial brings together research linking the gut microbiota to a range of conditions, from viral infections and respiratory diseases to cancer and neuropsychiatric disorders. It also highlights the therapeutic potential of dietary bioactive compounds and beneficial

microorganisms in immune modulation. Taken together, the editorial underscores the importance of maintaining a balanced microbiota as a comprehensive strategy to preserve health, including the health of the urogenital ecosystem.

Although the primary focus is the gut, the authors suggest broader implications. The immunological effects of the microbiota may extend to other mucosal environments, such as the vagina, by influencing epithelial integrity, pH regulation, and susceptibility to infections. Thus, the state of the gut microbiome may indirectly affect the composition and stability of the VM.

### 5.1. Gut microbiome metabolites and the diversity of the vaginal and urinary microbiota

The gut microbiome produces a variety of metabolites with systemic effects, including on the vaginal and urinary ecosystems. These compounds include short-chain fatty acids (SCFAs), β-glucuronidases, urolithins, and other bioactive metabolites, which can modify the composition and stability of microbiota in other body sites, thereby influencing urogenital health.[23]

β-glucuronidases, enzymes produced by the intestinal estrobolome, enable the reactivation of estrogens in the gut, promoting their recirculation and exerting beneficial local effects on the vaginal epithelium, pH, and microbial composition.[24]

SCFAs such as butyrate, propionate, and acetate—produced through the fermentation of dietary fibers—act as immunomodulators and enhance epithelial integrity, exerting anti-inflammatory effects. These fatty acids play a protective role by helping to preserve microbial balance in the vaginal and urinary tracts.[22] This improvement in mucosal function may reduce the migration of intestinal microorganisms toward the urogenital tract.[7,25]

Urolithins are metabolites produced by the gut microbiota from ellagitannins, compounds found in foods such as pomegranates and walnuts. Among them, urolithin A is excreted in the urine and may act directly on the bladder, possibly promoting a urinary ecosystem dominated by *Lactobacillus*.[22]

A deficiency of these metabolites—related to inadequate diet, gut dysbiosis, or menopause—is associated with a more diverse microbiota, loss of *Lactobacillus*, and an increased risk of infections.[7,25]

### 5.2. Gut microbiome and vaginal and urinary microbiota in menopause

The human microbiome plays a fundamental role in women's health, particularly in the regulation and defense of the urogenital tract. The interaction between the gut, vaginal, and urinary microbiomes has gained relevance in understanding conditions such as UTIs, overactive bladder (OAB) syndrome, and disorders related to the climacteric period.[22]

There is a functional connection between these three microbial ecosystems, and their disruption may predispose individuals to recurrent or chronic urinary diseases. After menopause, VM shows reduced *Lactobacillus* dominance and an increased presence of anaerobes and *Gardnerella vaginalis*, facilitating colonization of the lower urinary tract. In turn, the gut microbiome serves as a reservoir for uropathogenic bacteria, such as *Escherichia coli*, which can translocate and disturb the balance of the urobiome.[7]

This gut-vagina-bladder axis is regulated through shared immunological and metabolic networks. Factors such as diet, antibiotic use, age, and hormone levels exert a joint influence. A gut microbiota rich in *Lactobacillus* and Bifidobacterium species is associated with a lower risk of vaginal dysbiosis and recurrent cystitis, whereas its alteration may promote low-grade systemic inflammation, a condition commonly observed among postmenopausal women.[8]

In functional disorders such as OAB, the urinary microbiome is characterized by reduced *Lactobacillus* abundance and greater microbial diversity[25]—patterns that are often mirrored in the vaginal and gut microbiomes. These parallels support the existence of a shared microbial axis that modulates urogenital function.

The gut also plays a role in hormonal regulation through the estrobolome, a collection of bacterial genes capable of metabolizing estrogens.[24]

This microbiome-hormone axis is also implicated in the development of gynecological cancers. Alterations in the gut and VM can affect local immunity, promote chronic inflammation, and modify estrogen availability—factors that are all key to carcinogenesis.[26,27]

Overall, the gut, vaginal, and urinary microbiomes are closely interconnected. An integrated analysis of these ecosystems provides a more comprehensive understanding of urogenital diseases and opens new avenues for developing innovative, personalized therapeutic strategies in women's health.

## 6. Vaginal and urinary microbiome and interaction with the immune system in menopause

During menopause, hormonal changes induce profound remodeling of the urogenital tract, including alterations in

the vaginal and urinary microbiomes, as well as in local immunity. These synergistic changes have a significant impact on women's urogenital health during this stage, increasing the incidence of genitourinary symptoms, recurrent infections, and persistent inflammatory states.

Both the vaginal and urinary microbiomes exert immunomodulatory functions through interactions with the mucosal epithelium, resident immune cells, and soluble mediators such as cytokines, antimicrobial peptides, and immunoglobulins.

In states of eubiosis, *Lactobacillus* species predominate in the VM. The acidic environment they produce promotes the expression of antimicrobial peptides such as beta-defensin-2, which regulates the activation of pattern recognition receptors, including Toll-like receptor (TLR) 2 and TLR4, enabling the detection and control of pathogens.[3,11]

During postmenopause, the VM becomes less dominated by *Lactobacillus* and richer in anaerobic bacteria characteristic of CST IV, which favors genitourinary infections.[8] This microbial transition is accompanied by a less effective immune response, characterized by increased levels of inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, and decreased production of defensins and other innate antimicrobial molecules.[7,26]

The urinary microbiome also undergoes dysbiosis. A decline in *Lactobacillus* in both the vaginal and gut microbiota contributes to urinary symptoms such as dysuria, urgency, or recurrent infections.[25] Moreover, this dysbiosis may negatively modulate the activity of resident immune cells, such as macrophages and dendritic cells, compromising tissue homeostasis and promoting low-grade chronic inflammation.[27]

In summary, menopause leads to the loss of vaginal and urinary eubiosis, accompanied by an immune imbalance that favors chronic inflammatory states and recurrent pathologies.

## 7. Vaginal and urinary microbiota in genitourinary infections in menopause

### 7.1. Urinary infections

The study by Naji *et al.*[7] emphasizes the important contribution of the intestinal, vaginal, and urinary microbiomes in the origin and persistence of UTIs, particularly rUTIs in women. Disruptions in these microbial communities are thought to facilitate both the onset and recurrence of such infections. In women of reproductive age, the urinary microbiota is mainly composed of bacteria from the phylum *Firmicutes.*[28] Its composition and richness are influenced by variables such as age, hormonal status, ethnicity, and sexual behavior, all of which undergo significant changes during menopause.[29] At this stage, the reduction in *Lactobacillus* and changes in urinary microbial balance are linked to an increased risk of bladder dysbiosis, incontinence, and rUTIs.[28,29] Moreover, antibiotic treatments can disrupt the urinary microbiota, encouraging the growth of resistant uropathogens and the formation of biofilms—factors that contribute to persistent or recurrent infections.[30] The VM is also closely involved in rUTIs, as it shares several bacterial species with the urinary tract. The presence of *Lactobacillus* in the vagina is crucial for preventing the colonization of pathogens such as *E. coli*, a major cause of UTIs.[31] In women with vaginal dysbiosis or low *Lactobacillus* levels, especially during menopause, the risk of UTIs increases.[32] In addition, factors such as sexual activity and the use of vaginal douches can facilitate bacterial transfer between the vagina and urinary tract.

Estrogen replacement in postmenopausal women has been shown to reduce the incidence of UTIs by restoring *Lactobacillus* levels and promoting a healthy VM, thus lowering the risk of rUTIs.[7]

Probiotic therapies and the use of *L. crispatus* suppositories have shown promising potential in preventing rUTIs, although further research is needed to confirm their effectiveness.

The gut microbiome is also a key contributor to the development of UTIs, as bacteria residing in the intestine can translocate to the urinary tract and cause infections. Disruptions in gut microbial composition may influence both the vaginal and urinary microbiota, increasing susceptibility to UTIs. Natural defense mechanisms of the intestinal microbiota, such as the production of bacteriocins and SCFAs, help limit the growth of uropathogenic bacteria and reduce the likelihood of rUTIs.[33]

In this context, biotherapeutic strategies, including probiotics and fecal microbiota transplantation, have demonstrated encouraging outcomes in preventing rUTIs by reducing bacterial adhesion, impairing biofilm development, and enhancing host defenses.[34]

Recurrent UTIs are particularly prevalent in postmenopausal women, affecting over half of this population and significantly impacting quality of life, as well as increasing the risk of serious complications such as urosepsis. Recent studies using quantitative urine culture and *16S rRNA* gene sequencing in women over 55 years old with rUTIs (some receiving daily antibiotic prophylaxis and all on vaginal estrogen therapy [ET]) found no major differences in the total number of microbial species, including *Lactobacillus*.

However, genomic analysis revealed differences in specific bacterial populations, such as *Bacteroidales*, *Prevotella*ceae, and *Actinobacteria*. These findings underscore the need for further research to clarify the role of the urinary microbiome in rUTIs among postmenopausal women.[6] The rise in antimicrobial resistance has intensified efforts to develop strategies aimed at modifying the urogenital microbiota as a therapeutic approach for rUTIs. The interconnection between the vaginal and urinary microbiota is key, as both contain *Lactobacillus*, which offers protection against pathogens. Hormonal therapy with estrogens, both systemic and vaginal, has been associated with an increase in *Lactobacillus* abundance and a reduced incidence of rUTIs. However, in women with a history of rUTIs, a higher presence of pathogens and antimicrobial resistance genes has been observed, suggesting that microbiota alterations may contribute to infection persistence. In this regard, it has been shown that ET can modify the urogenital microbiota, promoting a healthier microbiota environment and protecting against rUTIs in postmenopausal women.[35] In summary, the intestinal, urinary, and vaginal microbiomes play an interconnected role in the pathogenesis of rUTIs in postmenopausal women. Therapies aimed at restoring microbiota balance, such as ET and probiotics, show promising potential for preventing and managing these infections.

### 7.2. VM and recurrent vaginal candidiasis

Vulvovaginal candidiasis (VVC) is one of the most common vaginal infections; however, there is limited data on its impact in postmenopausal women. The decline in estrogen levels during menopause alters the vaginal environment, increasing susceptibility to VVC. Nevertheless, the likelihood of developing VVC decreases by approximately 7% for each year after age 57, likely due to lower glycogen levels in these women. Factors such as medications (e.g., tamoxifen, antibiotics, HRT) and comorbidities like diabetes or immunosuppression can increase the prevalence of infection. Despite these associations, little research exists on the prevalence, risk factors, treatment, and recurrence of VVC in postmenopausal women. Given the changes in both the vaginal environment and the characteristics of *Candida* species, the disease is not accurately diagnosed, emphasizing the need for further studies and patient education to support appropriate treatment in this population.[36]

### 7.3. VM and BV - pathogenic mechanisms of *G. vaginalis*

G. *vaginalis* is included in CST IV of the VM, even among healthy women, complicating the interpretation of its role in the pathogenesis of BV. However, evidence suggests that G. *vaginalis* comprises virulent subtypes with distinct genetic and phenotypic characteristics. Recent research has identified 10 different strains, some of which produce β-galactosidase. Notably, strains that express the *sialidase a* gene are associated with BV and exhibit the ability to form biofilms. This enzyme cleaves sialic acid residues from glycoproteins in the vaginal mucus, exposing binding sites that facilitate G. *vaginalis* adhesion, support its nutrition acquisition, and protect it from host immune defenses. As a result, the bacteria can proliferate and compromise the protective mucosal barrier.[9]

A review by Daniel *et al.*[37] explored the association between intrauterine device (IUD) use and BV. Out of 1140 identified articles, 15 studies were included, comprising cross-sectional, case-control, cohort, quasi-experimental, and randomized trials. These studies examined BV prevalence in women using copper IUDs (Cu-IUDs) and levonorgestrel-releasing IUDs (LNG-IUDs), organizing the data into three categories: (i) point prevalence of BV among IUD users, (ii) incidence and prevalence of BV in Cu-IUD users, and (iii) incidence and prevalence in LNG-IUD users. The findings suggest that Cu-IUDs may increase the incidence of BV. However, there was insufficient evidence to establish a definitive relationship between LNG-IUD use and BV onset, largely due to variability in study designs and diagnostic criteria.

Vaginal dysbiosis, particularly BV, is associated with increased risk of acquiring urogenital infections, including STIs such as HIV. Studies have shown that women with a normal VM are less likely to contract HIV-1 than those with BV.[38]

### 7.4. Microbiota of the reproductive tract and PID

PID is an infection of the upper genital tract caused by pathogens ascending from the vagina and cervix, affecting the uterus, fallopian tubes, and ovaries. These pathogens may be endogenous, such as *Staphylococcus aureus*, *E. coli,* coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*, which are common in AV, or exogenous, mainly *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. BV is also associated with an increased risk of PID. Furthermore, dysbiosis in the VM, especially the decline in *Lactobacillus* species, facilitates the growth of pathogens and increases the likelihood of inflammation in the upper reproductive tract. Women with vaginal dysbiosis are at higher risk of bacterial colonization, which can lead to pelvic infections. It has been proposed that *Lactobacillus* protects the host by reducing the ability of *C. trachomatis* to infect epithelial cells.[39,40]

A prospective study investigating the microbiota of the upper and lower genital tracts in patients with acute

PID found an association between BV, AV, cervical inflammation, and PID. The study included both PID patients and a control group of women undergoing tubal sterilization. PID was diagnosed through laparoscopy, culdocentesis, ultrasonography, and endometrial biopsy, and microbiological cultures of abdominal and cervical samples were conducted to identify the causative microorganisms. In the PID patients, the most frequently isolated abdominal microorganisms included *Bacteroides*, *Peptostreptococcus*, *E. coli*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. Sexually transmitted pathogens such as *N. gonorrhoeae* and *C. trachomatis* were detected in 17% and 28% of patients, respectively. In the control group, no abdominal microorganisms were isolated. PID was attributed to endogenous bacteria in 48% of cases, and to sexually transmitted bacteria in 54%.[39]

A retrospective cohort study reported a higher incidence of PID among women diagnosed with BV. Among 2956 participants, the presence of BV, as determined by Nugent's score (adjusted hazard ratio [aHR] 1.53) and Amsel's criteria (aHR 2.15), and the use of vaginal douches (aHR 1.47) were independently associated with an increased risk of PID, regardless of sexual activity patterns or coexisting STIs.[41] Another study revealed an association between prolonged use of Cu-IUDs and the development of tubo-ovarian abscess (TOA) in postmenopausal women. Patients who had used an IUD for more than 10 years, without removal during menopause, showed a higher frequency of TOA and pelvic actinomycosis.[42]

Collectively, PID involves infection of the upper genital tract due to the ascending spread of pathogens linked to STIs, BV, and AV. Its development is influenced by factors such as genital tract inflammation, hormonal changes during menopause, and prolonged use of Cu-IUDs.

## 8. Vaginal and urinary microbiota in menopause and genitourinary syndrome

### 8.1. Clinical presentation

The GSM refers to a collection of symptoms associated with reduced estrogen levels that impact the genital, urinary, and sexual health of women. While it can arise at various stages of reproductive life, it is most frequently observed during menopause. Before 2014, terms like vulvovaginal atrophy, atrophic vaginitis, and urogenital atrophy were commonly used. That year, the North American Menopause Society and the International Society for the Study of Women's Sexual Health introduced the term GSM to provide a more accurate definition. VM, particularly *Lactobacillus* spp., is crucial for genital health, but its levels decrease with menopause due to reduced estrogen. GSM is a progressive condition affecting between 67% and 98% of postmenopausal women, with 50% presenting symptoms; however, only 32% seek medical help. These symptoms are often not recognized as being related to menopause.[43]

GSM can lead to complications such as labial atrophy, vaginal prolapse, introital stenosis, and urethral issues. It also negatively affects quality of life, emotional well-being, sexual function, and self-esteem. The VM plays a fundamental role in defending against infections and preserving gynecological health. A decline in *Lactobacillus* is linked to symptoms such as vulvovaginal atrophy and vaginal dryness. Estrogen contributes to symptom relief and helps restore *Lactobacillus* dominance in the vaginal environment, supporting genital tract protection and overall vaginal well-being.[43]

### 8.2. Microbiota in GSM

Several investigations have explored the relationship between the VM and GSM. A 2-year follow-up study involving 750 women aged 35–60 revealed that postmenopausal women had a higher prevalence (49.7%) of vaginal microbial communities with low *Lactobacillus* levels, in contrast to 21.2% in premenopausal and 22.9% in perimenopausal women. Vaginal environments dominated by species like *L. crispatus*, *L. gasseri*/*jensenii*, and *L. iners* were linked to a lower likelihood of developing vaginal atrophy. In addition, *L. gasseri*/*jensenii* in postmenopausal women was associated with fewer symptoms of vaginal dryness and reduced libido, indicating the potential role of VM in managing and preventing GSM, especially after menopause.[44] In a separate cross-sectional analysis of 96 peri- and postmenopausal women, researchers examined the role of vaginal dysbiosis in GUSM. Among participants, 83.58% reported symptoms associated with the condition, and a greater microbial variety was observed in postmenopausal individuals. A decline in *Lactobacillus* levels correlated with both the onset and intensity of GUSM symptoms. Other microorganisms, including *E. coli*, *Shigella*, *Anaerococcus*, *Finegoldia*, *Enterococcus*, *Peptoniphilus* harei, and *Streptococcus*, were linked to genital and sexual complaints. Supplementation with *Lactobacillus* was found to ease genital discomfort and enhance sexual function, suggesting it could offer a non-hormonal therapeutic option for addressing GSM symptoms.[45]

### 8.3. GSM treatment

Managing GSM poses challenges due to the broad spectrum of available therapies and the necessity to tailor treatment to each patient's specific clinical profile. As noted by Cuccu *et al.*,[46] initial strategies typically involve the use of vaginal lubricants and moisturizers, particularly in cases of mild to moderate discomfort. In situations

where symptoms are more intense, hormonal treatment options are generally indicated. Topical hormonal options, such as vaginal creams, are preferred due to their lower risk of side effects compared to systemic treatments. Notable options include ospemifene and dehydroepiandrosterone (DHEA), which improve vaginal and urinary symptoms without significantly altering systemic estrogen levels.

Although hormone therapy is beneficial, it carries potential risks, particularly for women with a personal history of cancer or who are considered at elevated risk. The safety of these treatments remains a controversial topic, requiring further research, particularly in women with a history of breast cancer. It is crucial for physicians to consider the benefit-risk profile of each patient before prescribing hormonal treatments and to promote informed decisions based on available evidence.[46]

A multicenter study carried out across 28 sites in Spain involving 108 postmenopausal women found that using 0.005% vaginal estriol gel was effective in lowering the recurrence of UTIs. Participants treated with estriol experienced a notable decline in infection rates and an improvement in vaginal pH, supporting its potential as a safe and beneficial therapy for postmenopausal women affected by GSM.[47] Over the years, multiple clinical guidelines have addressed the treatment of this condition. The United States Food and Drug Administration (FDA) has authorized various therapies for managing vulvovaginal atrophy and vasomotor symptoms linked to menopause. Nonetheless, the FDA has also issued warnings about the potential risks of hormone therapy, including increased risks of cardiovascular events, breast cancer, and thromboembolism. These concerns led many women to discontinue systemic hormone treatment following the findings from the Women's Health Initiative.[43] For pharmacological treatments, systemic ET is the main option for vasomotor symptoms, while local ET is used for vaginal symptoms. Vaginal ET is considered the first-line treatment for GSM, as it involves lower doses and has fewer side effects. In women who have undergone hysterectomy, only estrogen is used, whereas in those with an intact uterus, it is combined with progestogens.[43]

DHEA, also known as prasterone, is effective for treating dyspareunia (pain during sexual intercourse) and other GSM symptoms. DHEA improves vaginal lubrication and epithelial function without affecting systemic estrogen levels. Ospemifene, a selective estrogen receptor modulator, is also effective in treating dyspareunia and vaginal dryness, offering beneficial effects on bones and anti-estrogenic effects on breast tissue.[43]

Estriol, a naturally occurring estrogen with mild potency, is commonly employed in countries outside the United States for managing GSM. Despite lacking FDA approval, its application as a vaginal gel has demonstrated positive effects on the vaginal maturation index and pH levels in postmenopausal women. The combination of estriol with *Lactobacillus acidophilus* has been reported to improve GSM symptoms and support the recovery of VM. In women with a personal history of breast cancer, hormonal therapies should generally be avoided. In these cases, non-hormonal alternatives such as lubricants, hyaluronic acid, pelvic floor therapy, and laser-based treatments offer reasonable and safe options.[43] Emerging research indicates that probiotics, either alone or used alongside ET, can help relieve symptoms of vulvovaginal atrophy. In postmenopausal women, oral probiotics like *Lactobacillus rhamnosus* Gr-1 and *Lactobacillus reuteri* RC-14 were associated with significant reductions in Nugent scores and notable improvements in GSM symptoms ($p$=0.0001). Another study found that the use of estrogen together with probiotics was especially beneficial for symptoms like vaginal dryness and painful intercourse. In ovariectomized rat models, supplementation with *Lactobacillus* decreased menopausal symptoms and enhanced intestinal barrier function.[48] Altogether, VM is crucial for genital health and is related to GSM. Estrogen deficiency in menopause reduces *Lactobacillus*, leading to symptoms such as vaginal dryness and urinary issues. Vaginal dysbiosis, characterized by fewer *Lactobacillus* and more pathogenic bacteria, exacerbates symptoms. Management strategies encompass vaginal estrogen formulations, ospemifene, DHEA, and estriol, along with non-hormonal therapies suitable for women diagnosed with breast cancer. Among the non-hormonal alternatives, laser-based treatments and *Lactobacillus* supplementation have demonstrated encouraging outcomes.

## 9. Vaginal and urinary microbiota in menopause and pelvic floor disorders

A systematic review[49] explored the influence of the microbiome on female reproductive and urological health, addressing conditions such as urinary incontinence, OAB, pelvic pain, fecal incontinence, and hypoactive sexual desire disorder. It underscores the relevance of microbial species like *Lactobacillus*, which are key to preserving microbial homeostasis. A significant association was observed between symptom severity in OAB and increased microbial richness and diversity. Genera including *Lactobacillus*, *Streptococcus*, *Gardnerella*, *Prevotella*, *Methylobacterium*, *Acinetobacter*, and *Sphingomonas* were linked to the intensity of OAB-related symptoms, suggesting a connection between bladder microbiota composition and clinical manifestations.[50] The work highlights how variations in microbial composition

between healthy individuals and those with certain conditions may offer diagnostic value. Specific bacterial profiles could act as indicators for disorders such as endometriosis and urinary incontinence. Adjusting the microbiota using probiotics or comparable methods is proposed as a possible therapeutic approach. Moreover, the relationship between microbial diversity and symptom severity is highlighted, as greater bacterial diversity might increase the severity of conditions.[49] The included studies utilized sophisticated methods, including *16S rRNA* gene analysis and focused metabolic profiling, which have contributed to a deeper understanding of the microbiome. It underscores the importance of a personalized treatment approach based on individual microbial differences. However, an important gap is identified—the lack of causal evidence between changes in the microbiome and pelvic floor dysfunctions. Longitudinal studies manipulating the microbiome to assess its direct effects on these dysfunctions are suggested.[49]

One study explored how the urinary and VM are linked to the intensity of mixed urinary incontinence (MUI) symptoms in women.[51] The study included 210 participants, with 126 diagnosed with MUI and 84 serving as controls. Researchers identified six distinct urinary microbiome profiles; one group, characterized by low *Lactobacillus* levels and increased microbial diversity, was correlated with more frequent and intense episodes of total and urgency incontinence. The reference group, dominated by *Lactobacillus*, showed less severe symptoms. Although vaginal community types were not related to the severity of incontinence, alpha diversity in urine showed that greater bacterial richness was associated with more incontinence episodes. The results suggest that lower *Lactobacillus* dominance and higher bacterial diversity may be linked to greater severity of urinary incontinence, but more research is needed to determine whether other bacterial genera also play a role.[51]

Before 2012, it was commonly assumed that the urinary tract of healthy individuals was sterile. However, metagenomic analysis has uncovered the presence of a distinct urinary microbiota, reshaping the understanding of lower urinary tract disorders (LUTD). Alterations in this microbial community, termed urinary dysbiosis, have emerged as a possible contributing factor to functional LUTD. A review encompassing 36 studies found that viable bacteria present in urine, but undetectable through traditional cultures, may play a central role in dysbiosis.[52] An important observation is that women experiencing OAB present distinct urinary microbial profiles when compared to asymptomatic women. Notably, there is a higher presence of genera like *Gardnerella* and a reduced abundance of *Lactobacillus*, indicating that such microbial imbalances may play a significant role in the development of OAB manifestations, particularly urgency in the absence of infection.[53] This pattern is also seen in urgency urinary incontinence, where urinary dysbiosis may influence bladder storage symptoms. Research has shown 80% bacterial growth in women with OAB, undetected by standard cultures, highlighting the need to improve diagnostic methods.[53]

Emerging evidence suggests that urinary microbiota may be pivotal in tailoring individualized therapies for women affected by urgency urinary incontinence, allowing more precise classification of subtypes and optimizing treatment strategies. This underscores the growing recognition of the microbiome's role in the development and management of urinary tract conditions.[54] In contrast, the systematic review conducted by Sze *et al.*[25] examined the relationship between dysbiosis in the gut, vagina, and urinary tract in women diagnosed with OAB. While a consistent bacterial profile was not observed among healthy participants, OAB patients displayed reduced microbial diversity. Although the overall bacterial composition between cases and controls did not differ significantly, the urinary microbiome of those with OAB appeared more susceptible to changes influenced by the intestinal or vaginal environment. These findings point to a possible interconnection between the three microbial ecosystems, but further studies are needed to clarify this association.[25]

In addition, Yu *et al.*[55] carried out a meta-analysis including 7298 Chinese women across eight studies, exploring the relationship between pelvic floor disorders and vaginal microbial alterations. The results indicated that a reduced presence of *Lactobacillus*, increased vaginal discharge, and a history of vaginitis were linked to higher pelvic floor disorder risk. The review highlights that imbalances in the VM may lead to inflammation and damage to pelvic support tissues, potentially contributing to the onset of pelvic organ prolapse. This condition results from weakening of the pelvic structures—ligaments, muscles, and connective tissue—often influenced by changes in extracellular matrix components such as collagen, elastin, and proteoglycans, all synthesized by fibroblasts and crucial for pelvic stability.

In summary, the urinary and VM play a significant role in women's urogenital and reproductive well-being during menopause. Variations in microbial diversity within these ecosystems have been associated with conditions such as urinary incontinence and OAB. Although notable associations have been reported, further studies are required to confirm causality. Modulating the microbiome, including through probiotic interventions, holds promise

as a preventive and therapeutic option for urinary and pelvic floor disorders.

## 10. Vaginal and urinary microbiota in menopause and gynecological cancer

The female reproductive tract contains a specialized microbiome crucial for maintaining health, especially in the lower tract, where *Lactobacillus* species dominate during the reproductive years. These bacteria interact beneficially with the host, preserving vaginal balance. When this harmony is disrupted, known as dysbiosis, it can impair immune and metabolic pathways, leading to processes associated with malignancy, such as persistent inflammation, genomic instability, and altered metabolism.[56-58] These disruptions may contribute to the onset and progression of gynecologic cancers, including cervical, ovarian, and endometrial cancers, potentially through both indirect and direct mechanisms.[56] While the involvement of specific bacterial pathogens in these cancers remains uncertain, broad shifts in microbial composition have been linked to tumorigenesis.[26] Multiple risk factors are implicated in these cancers, including STIs (human papillomavirus [HPV], *C. trachomatis*, HIV), use of postmenopausal hormones, obesity, tobacco use, and inherited genetic predispositions. More recently, research has started exploring how human-associated microbial communities might influence cancer development in the reproductive tract. Although it is still unclear whether microbial alterations are a driving factor or a byproduct of these malignancies, increasing data support the notion that the microbiota may foster tumorigenesis through mechanisms such as reduced apoptosis, enhanced cell proliferation, and genomic instability.[26,57]

The urogenital microbiota, influenced by factors such as sex and age, also plays an important role in gynecological carcinogenesis. In women with low estrogen levels, such as those before puberty or postmenopausal, a mixture of anaerobic bacteria predominates, potentially creating a less protective environment against infections and cellular alterations. In contrast, during pregnancy or in young women with high estrogen levels, the VM remains more stable and is dominated by *Lactobacillus*, which protects the reproductive tract against pathogens and reduces the risk of gynecological cancers.[56] Harmful bacteria significantly contribute to the weakening of the epithelial barrier by producing hydrolytic enzymes and promoting the release of proinflammatory cytokines like IL-6 and TNF.[58] These actions drive chronic inflammation and disturb local metabolic processes, creating conditions that may support carcinogenesis. They also induce genetic instability by either damaging DNA directly or interfering with its repair, thereby increasing mutation risk. This may lead to the activation of molecules such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which suppress programmed cell death and stimulate blood vessel formation, both of which are critical to tumor progression. Moreover, microbial metabolites from the gut, including deoxycholic acid and lipoteichoic acid, can circulate through the body and contribute to the emergence of cancers in distant organs, such as the liver.[26,59,60]

Various pathogenic bacteria are linked to carcinogenesis. For example, *Helicobacter pylori* is associated with gastric cancer,[61] while *Fusobacterium nucleatum* has been linked to colon cancer.[62] Research in animal models has shown that reducing the microbiota through antibiotics decreases tumor formation in organs such as the colon and liver, suggesting that a dysbiotic microbiota may promote tumor development.[26]

Alterations in microbial balance have also been associated with the initiation and development of tumors in other parts of the body, including the skin, mouth, respiratory system, and reproductive tract. Dysbiotic microorganisms can cause failures in the epithelial barrier, immune dysregulation, and genotoxicity, creating a microenvironment conducive to cancer. Chronic inflammation is one of the best-documented mechanisms modulating cancer characteristics. For instance, *F. nucleatum* in colorectal cancer activates the NF-κB pathway, promoting the production of inflammatory cytokines such as IL-6 and TNF, which in turn promote cell proliferation and angiogenesis, both of which are essential characteristics of cancer.[56]

*C. trachomatis* has been identified as one of the bacteria involved in the development of gynecologic cancers. It facilitates tumor initiation by triggering epithelial-mesenchymal transition, which reduces cell adhesion and disrupts mechanisms that repair DNA damage.[63] In addition, the interplay between the gut and VM can modulate estrogen concentrations, influencing hormone-dependent disorders like endometriosis and specific cancers. The estrobolome, comprising microbial genes responsible for estrogen metabolism, controls circulating estrogen levels via β-glucuronidase activity. Dysbiosis can interfere with this regulation, leading to hormonal imbalances that may contribute to gynecologic conditions.[64] Beyond its impact on cancer development, the microbiota also plays a role in treatment outcomes among women with gynecologic malignancies. Anticancer strategies, including chemotherapy and radiotherapy, can disrupt microbial communities, potentially affecting treatment effectiveness and side effects. Interventions such as probiotics or fecal microbiota transplantation

offer the potential to enhance therapeutic efficacy and improve patients' quality of life by restoring microbial equilibrium.[56] Research in this field is crucial as it could open new opportunities for the prevention and treatment of these cancers, improving clinical outcomes and the quality of life for affected patients.[56]

### 10.1. VM and cervical cancer: Role of HPV

Cervical cancer remains one of the leading malignant tumors affecting women and ranks fourth in global incidence, with around 342,000 deaths recorded in 2020.[26] More than 95% of cases are attributed to persistent infection with HPV.[65] Although cervical cancer affects women worldwide, disparities exist between racial and ethnic groups. For instance, Hispanic women in the United States face a 60% higher likelihood of being diagnosed and a 30% greater mortality rate than non-Hispanic white women.[66] Oncogenic strains such as HPV-16 and HPV-18 are the primary contributors to cervical cancer development.[26,56] The cervical transformation zone, where squamous and columnar cells meet, is particularly vulnerable to HPV and is the origin site for most cervical malignancies.[67] While many infections are cleared by the immune system, approximately 10–15% persist and may evolve into cervical intraepithelial neoplasia or invasive cervical cancer.[26] Several cofactors, including multiple births, tobacco use, hormonal contraceptive use, and coinfections with other sexually transmitted pathogens, increase the risk of disease progression.[56]

Recent investigations have emphasized the significant role of the VM in influencing the persistence of HPV infections and the development of cervical cancer. This association appears especially relevant among Hispanic women, who often present with reduced *Lactobacillus* dominance and increased vaginal pH—factors that may partly explain the higher incidence and mortality from cervical cancer observed in this population.[67] A meta-analysis based on longitudinal data supports the hypothesis that a vaginal microbial environment with high diversity and lacking *Lactobacillus* predominance favors the acquisition and persistence of HPV, as well as the development of precancerous cervical lesions.[56] Specifically, women whose microbiota is primarily composed of *L. iners* show a greater tendency toward persistent infection by high-risk HPV types and progression to malignancy compared to those dominated by *L. crispatus*. This may be due to the diminished protective function of *L. iners*, including its weaker ability to suppress harmful microbes and lower lactic acid production, which contributes to a microenvironment conducive to HPV survival and cervical neoplastic changes.[56] Disruption of the vaginal microbial balance, known as vaginal dysbiosis, significantly contributes to HPV persistence. This microbial imbalance fosters an inflammatory milieu that supports viral transformation, including the upregulation of oncogenic proteins like E6 and E7,[68] promotion of genomic instability, and activation of telomerase—processes central to cervical carcinogenesis. In addition, women whose VM is predominantly composed of *L. iners* have demonstrated increased concentrations of inflammatory cytokines such as TNF-α, IL-1α, interferon gamma, and IL-8, further illustrating the link between dysbiosis and heightened susceptibility to cervical abnormalities.[69]

*C. trachomatis* infection has also been implicated in enhancing HPV persistence and its progression to precancerous changes by disrupting epithelial integrity, increasing basal cell exposure to HPV, and triggering anti-apoptotic pathways that support ongoing infection.[70] Supporting this evidence, recent studies underscore the role of VM in cervical pathology. BV, characterized by a depletion of *Lactobacillus* species and an overgrowth of anaerobic bacteria, has been linked to increased susceptibility to HPV infection and reduced viral clearance. A greater diversity of non-*Lactobacillus* bacteria has been associated with persistent HPV infection and progression toward high-grade cervical intraepithelial neoplasia.[71] Cross-sectional analyses indicate that HPV-positive women without dysplasia tend to exhibit a more heterogeneous VM, with higher prevalence of BV-related bacteria such as *Gardnerella*, *Sneathia*, *Megasphaera*, *Dialister*, and *Atopobium* compared to HPV-negative women.[72,73] Furthermore, longitudinal data suggest that *L. gasseri* may facilitate viral clearance, whereas *Atopobium* species are more frequently associated with sustained HPV infection.[74] A decrease in *Lactobacillus* abundance and increased microbial diversity have also been associated with elevated vaginal pH, a condition linked to more severe cervical lesions.[73]

Taken together, these findings highlight the key role of the VM in HPV persistence and cervical oncogenesis. An imbalanced microbiota, particularly when dominated by *L. iners* and BV-associated anaerobes, promotes a proinflammatory state that supports viral persistence and transformation. Understanding these microbial dynamics is essential for advancing both prevention and therapeutic strategies targeting cervical cancer.

### 10.2. VM and endometrial cancer

Endometrial cancer predominantly affects women after menopause, especially those in their 60s and 70s. It ranks as the leading gynecological malignancy in developed nations and is particularly common among women in the United States. Although genetic and hereditary mutations account for only 10–20% of cases, sociodemographic

elements such as race, ethnicity, and economic status may elevate the risk.[56] In the United States, both Black and non-Hispanic White women exhibit high incidence rates of this disease; however, African American women face nearly double the mortality rate compared to other racial groups.[56,75] Key contributing factors include obesity, chronic inflammation, disruptions in estrogen pathways, and the use of ET after menopause. These elements are associated with alterations in both the gut[76] and VM,[77] indicating that microbial changes may play a role in the pathogenesis of endometrial cancer.[56] Obesity contributes to endometrial cancer development through multiple biological pathways, including elevated insulin levels and increased bioavailability of insulin-like growth factor 1, both of which stimulate cellular growth and reduce programmed cell death in the endometrium.[26,78] This condition is a major contributor to the rising incidence of endometrial cancer, partly due to enhanced estrogen synthesis by adipose tissue, which drives endometrial cell division and tumor progression.[78] Estrogens also play a critical role, reinforcing how external influences such as high-fat diets are associated with a heightened risk of the disease. While ET may help relieve menopausal symptoms, it has also been linked to a greater likelihood of developing endometrial cancer.[26,78] Recent studies have suggested that both the intestinal and VM could be indirect risk factors, highlighting their importance in the etiology of the disease.[79] In summary, endometrial cancer is a multifactorial disease in which genetic, hormonal, environmental, and microbiological components interact, underscoring the need for preventive and therapeutic approaches that consider this complex interaction of factors.

The long-held belief that the uterine cavity was sterile has been questioned by several studies using 16S rRNA sequencing, which confirmed the existence of a resident microbiota. Microorganisms may reach the uterus through hematogenous spread, ascend from the lower genital tract during different menstrual phases, or be introduced during gynecological interventions such as assisted reproductive technologies.[80] Compared to the vagina; the microbiota of the upper genital tract is less abundant but more diverse, whereas the vaginal flora is primarily dominated by *Lactobacillus* species.[81]

Chen *et al.*[82] reported that the composition of the microbiota differs along the female reproductive tract and undergoes fluctuations depending on the menstrual cycle phase. During the secretory phase, there is a notable increase in microbial presence, especially *Propionibacterium acnes*, along with heightened metabolic activity involving purines, pyrimidines, amino acids, and peptidoglycan synthesis. Furthermore, certain vaginal bacterial species such as *Prevotella*, *Porphyromonas*, *Firmicutes*, *Spirochaetes*, *Atopobium*, and *Bacteroides*, in combination with elevated vaginal pH, have been linked to the development of endometrial cancer.[56,77,83,84] These microorganisms trigger the production of proinflammatory cytokines like IL-1α, IL-1β, IL-17α, and TNFα, which are commonly overexpressed in various malignancies, including those of the endometrium. IL-17α in particular has been shown to stimulate endometrial cell growth and facilitate the progression of endometriosis through its role in promoting inflammation and angiogenesis.[26,85] Recent studies indicate that the gut-brain axis plays a role in controlling circulating estrogen levels, involving the "estrobolome," a collection of bacteria capable of modifying estrogen enterohepatic circulation.[86] These bacteria produce β-glucuronidase, an enzyme that reactivates estrogens, enabling their interaction with receptors and influencing estrogen-dependent biological functions.[24,26] Disruptions in the estrobolome, or dysbiosis, can cause imbalances that contribute to diseases, including cancer. Research has identified a distinct microbial profile in endometrial cancer tissues compared to adjacent non-cancerous tissue, with higher amounts of genera like *Prevotella*, *Atopobium*, and *Porphyromonas* in tumor tissues, while *Lactobacillus* predominates in surrounding tissues.[87] In addition, elevated *Prevotella* levels and increased D-dimer in cancer tissue have been linked to more advanced disease and poorer outcomes.[26] Various explanations for bacterial overgrowth in endometrial cancer include changes in the tissue environment that promote bacterial proliferation, weakened immune defenses, or altered bacterial adherence and colonization. These observations suggest that the microbiota may influence the development, etiology, and progression of endometrial cancer, a field that requires further investigation.

### 10.3. Microbiota and ovarian cancer

Ovarian cancer is the second most common cancer in women, with more than 313,000 new cases and 152,000 deaths in 2020.[26] The incidence varies across different demographic groups, being highest among non-Hispanic White women (11.6/100,000), followed by Native American, Hispanic, non-Hispanic Black, and Asian and Pacific Islander women.[87] The lack of specific symptoms often delays diagnosis, leading to 70% of cases being detected at advanced stages. Incidence increases in postmenopausal women, with various factors contributing to the risk.[26]

#### *10.3.1. Risk factors*

Recent investigations suggest that microbial communities may play a role in the onset and development of ovarian

cancer, though establishing direct causality remains challenging due to the complex interplay of multiple contributing factors and the high variability of individual microbiomes.[88]

Hormonal influences such as not having given birth, early onset of menstruation, and late menopause are associated with an elevated risk. In contrast, pregnancy and oral contraceptive use offer protective effects by limiting ovulatory cycles.[26] Oral contraceptives also influence the expression of transforming growth factor β isoforms, triggering apoptosis in ovarian epithelial cells. Environmental exposures, including diets high in animal fats and Westernized lifestyles, may increase susceptibility, while diets rich in vegetables are linked to reduced risk. Genetically, although most ovarian cancer cases are sporadic, about 10% are inherited. Mutations in the *BRCA1* and *BRCA2* genes are major contributors, conferring a 20–40% lifetime risk for *BRCA1* mutation carriers and a 10–20% for *BRCA2* carriers.[26] Having multiple pregnancies, undergoing tubal ligation, or using oral contraceptives has been shown to lower the risk of ovarian cancer.[56]

#### *10.3.2. Oncobiome or the interaction between the human microbiome and carcinogenesis*

The concept of oncobiosis refers to the interplay between the human microbiome and the development of cancer, and it has been observed in several anatomical sites, including the vaginal and cervicovaginal regions, the upper genital tract, ovaries, tumor tissue, peritoneal cavity, bloodstream, and fecal matter. This microbial imbalance is linked to a reduction in microbial diversity, particularly in the peritoneal and intratumoral microbiomes found in ovarian cancer cases.[88,89] Analyses of tumor specimens revealed a predominance of bacterial phyla such as *Proteobacteria* and *Firmicutes* compared to non-cancerous tissues.[88-91] These microbes can secrete genotoxins like colibactin and cytotoxic distending toxins, which cause DNA damage and trigger repair mechanisms.[26] Moreover, a decrease in microbial diversity has been observed in cancer cases, suggesting that changes in the microbiota could influence disease development.[26,88,91] On the other hand, a study revealed that malignant epithelial ovarian tumors harbored a more diverse and abundant microbiota, including members of the order Actinomycetales as well as genera such as *Acinetobacter*, *Streptococcus*, *Ochrobacterium*, and *Pseudomonas.*[92] They also identified that *P. acnes* might accelerate cancer development.

In the vagina, a low abundance of *Lactobacillus* is associated with ovarian cancer and *BRCA* mutations,[93] especially in younger patients.[94] Genital infections, such as *C. trachomatis* and *N. gonorrhoeae*, increase the risk of ovarian cancer,[93] as well as viral infections such as HPV, cytomegalovirus, Epstein-Barr virus, and HIV.[26,56,84] In addition, antibodies against *C. trachomatis* may be associated with a higher risk of ovarian cancer by promoting the survival of cells with damaged DNA.[95] Some microorganisms invade the tumor, generating an "intratumoral microbiota" that contributes to cancer progression through mutations in DNA, activation of carcinogenic pathways, and metastasis. Certain bacterial components, including *E. coli* lipopolysaccharide found in the VM, can trigger pro-inflammatory cytokine production, which supports tumor progression and resistance to chemotherapy.[26] Inflammation within the genital tract has been linked to carcinogenesis, as seen in PID, a recognized risk factor for ovarian cancer.[56] An imbalance in the VM—marked by a decline in *Lactobacillus* species and an increase in genera such as *Acinetobacter*, *Burkholderia*, G. *vaginalis*, and *Prevotella*—may promote a local environment prone to inflammation and malignancy. This alteration appears to be associated with metabolic shifts involving glycerophospholipids and tryptophan, which, in murine models, contribute to ovarian tumor development.[56,96] Local inflammation, induced by bacterial colonization, can promote carcinogenesis by activating pattern recognition receptors such as TLR2, 4, and 5, which respond to Gram-negative bacteria. The activation of these receptors triggers inflammation through signaling pathways like NF-κB, which favors oncogenesis. Tumor-associated macrophages are essential for the development of ovarian cancer,[93] and peritoneal colonization can drive metastasis formation, including interaction with the intestinal microbiome, promoting spread to the gastrointestinal tract.[56,88] Moreover, the microbiome affects the response to treatments such as chemotherapy. Modifying the microbiome with antibiotics, probiotics, and nutrients could be a promising therapeutic and diagnostic strategy.[89]

#### *10.3.3. Summary*

Research on the microbiota and ovarian cancer has identified a significant relationship between microbial alteration and disease progression. Dysbiosis affects areas such as the vagina, genital tract, tumor tissue, and intestines, contributing to the initiation and progression of cancer. Bacteria such as *Proteobacteria* and *Firmicutes* predominate in these tissues, and bacterial infections such as *C. trachomatis* and *N. gonorrhoeae* increase cancer risk. The reduction of *Lactobacillus* in women with *BRCA* mutations may be a key factor. Bacterial metabolites induce chronic inflammation, suggesting the use of probiotics and antibiotics as potential treatments.

## 11. Vaginal and urinary microbiota in menopause and periodontal disease

Periodontal disease, encompassing both gingivitis and periodontitis, is a chronic infection resulting from the build-up of bacterial plaque on the tooth surface.[97] This condition involves a persistent inflammatory response that affects the tissues supporting the teeth, including the gums, periodontal ligament, and alveolar bone.[97] It has a complex origin, but key pathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are recognized as major contributors.[98-100] The interaction between these microorganisms and the host immune defense can trigger tissue breakdown and ultimately result in tooth loss. In addition, the disease can introduce anaerobic Gram-negative bacteria, toxins, lipopolysaccharides, and proinflammatory substances into the circulation, potentially influencing the onset or progression of systemic conditions. Menopause, associated with a decrease in hormone levels, particularly estrogen, has been identified as a risk factor for periodontal deterioration. Studies have shown that postmenopausal women have a higher prevalence of periodontal disease, which could be linked to increased systemic inflammation and hormonal changes that affect both vaginal and oral microbiota.[97,101]

A study from India found a link between menopause, periodontal tissue damage, and osteoporosis. When comparing premenopausal and postmenopausal women, measurements such as dental plaque, gingival inflammation, probing depth, and clinical attachment loss were significantly higher in postmenopausal women ($p$=0.01). These findings suggest that women after menopause have an increased risk of periodontitis, highlighting the need for preventive care and timely treatment of oral conditions.[97] In addition, another study concluded that steroid sex hormones, particularly estrogen, play a crucial role in modulating periodontal tissue responses to bacterial plaque. The decline in estrogen during menopause could alter these responses and contribute to the development of periodontal disease.[101] Although it is known that estrogen deficiency is associated with bone loss in the periodontium, the exact mechanism by which this deficiency leads to bone loss remains an area of research.[102]

The relationship between the VM and periodontal health has been increasingly recognized. Although they belong to different biological systems, it has been suggested that both microbiota could influence each other due to the interconnectedness of inflammatory processes.[103] Several studies indicate that dysbiosis in the VM, especially during menopause, can induce a systemic inflammatory response that affects not only the genital tract but also other tissues such as the gums, promoting the progression of periodontitis.[97,101]

In addition, certain bacteria frequently found in both the oral cavity and VM, including *P. gingivalis* and *F. nucleatum*, are linked to periodontal disease and may also colonize the vaginal environment.[98-100,103] This suggests that infections originating in the mouth might affect the VM, potentially impacting women's reproductive and gynecological health. BV and periodontal disease both involve an imbalance in microbial communities, known as dysbiosis. These conditions have been linked to a higher risk of pregnancy complications, although a clear causal link remains unproven. Research involving South African adolescent girls found that bacteria commonly linked to periodontal disease, including *Prevotella intermedia* and *Porphyromonas endodontalis*, were present in greater amounts in the oral microbiota of those with disrupted VM. This points to a potential connection between oral and vaginal microbial imbalances, highlighting the need for further studies to clarify any causal relationship.[104]

In a study conducted at the Hospital Clínico San Borja Arriarán, which included pregnant women with preterm labor before 34 weeks of gestation, a prevalence of periodontal disease of 93.2% was found. Furthermore, 27.1% of patients showed microbial invasion of the amniotic fluid, with 18.6% associated with periodontal pathogenic bacteria. Cervicovaginal infection was observed in 83.1% of patients, with BV present in 23.7%. Among the women with cervicovaginal infection, 72.9% also had periodontal disease. Preterm birth (<37 weeks) occurred in 64.4% of the patients and was significantly associated with generalized periodontal disease and the concurrent presence of ascending bacterial infection and periodontal disease. In addition, patients with preterm birth and generalized periodontal disease showed a higher frequency of chorioamnionitis and funisitis, suggesting that infection contributed to preterm labor.[99] This study highlights the interaction and importance of the periodontal and VM in pregnant women. This relationship is likely to be no different in postmenopausal women.

### 11.1. Biological mechanisms linking periodontal disease with genital microbiota

Several biological mechanisms have been proposed to explain the link between genital microbiota dysbiosis and periodontal disease, particularly in postmenopausal women:

(i) Systemic inflammation: Dysbiosis in the VM during menopause can induce a systemic inflammatory response that affects other tissues, including the gums, promoting the progression of periodontitis.[103]

**Table 1. Pathologies associated with menopause and microbiota alteration**

| Pathology (references) | Microbiota alteration |
|---|---|
| Recurrent urinary tract infection[28-30,32,33] | Decrease in *Lactobacillus* spp. in the vagina and reduction in SCFAs and intestinal bacteriocins, which normally inhibit uropathogen growth in the vagina and bladder |
| Bacterial vaginosis[37,38] | Decrease in *Lactobacillus* spp. and increas e in anaerobes such as *Gardnerella vaginalis*, which expresses sialidase A—enhancing bacterial adhesion, biofilm formation, and compromising vaginal defenses |
| Pelvic inflammatory disease[39-41] | Decrease in *Lactobacillus* spp.; increase in endogenous pathogens (*Escherichia coli*, *Staphylococcus*) and exogenous ones (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*). BV promotes bacterial colonization and persistent inflammation, enabling ascending infections |
| Genitourinary syndrome of menopause[43-45] | Significant decrease in *Lactobacillus gasseri/jensenii* and *Lactobacillus crispatus*, contributing to vaginal atrophy, dryness, and sexual dysfunction. Increased microbial diversity with the presence of *E. coli*, *Shigella*, and *Streptococcus,* causing genital symptoms |
| Pelvic floor disorders—OAB, UI, POP[49-55] | Decrease in *Lactobacillus* spp. and increase in vaginal microbial diversity are associated with OAB and UI. Inflammation weakens pelvic connective tissue, favoring POP. Associations exist, but more research is needed to establish causal links |
| Gynecological cáncer[56-58,64] | Decrease in *Lactobacillus* spp. and increase in anaerobic vaginal bacteria promote dysbiosis, chronic inflammation, genetic instability, metabolic dysfunction, and cell proliferation. Disruption of the estrobolome reduces estrogen levels |
| Cervical cancer[56,68-74] | Loss of *Lactobacillus* promotes HPV persistence and cancer progression. Dominance of *Lactobacillus iners* facilitates inflammation, oncoprotein expression, and poor HPV clearance. BV with *Gardnerella* and *Atopobium* is linked to dysplasia |
| Endometrial cancer[56,76,77,79,83,84,86,87] | BV and the genera *Prevotella*, *Porphyromonas*, and *Atopobium* drive chronic inflammation and cancer. Induction of IL-1β and TNF-α promotes proliferation and angiogenesis. Estrobolome is disrupted |
| Ovarian cancer[88-96] | BV and the genera *Acinetobacter*, *Gardnerella*, and *Prevotella* are associated with inflammation and cancer. Dysbiosis in peritoneum and tumor tissue, with reduced microbial diversity, activates NF-κB. Intratumoral *Proteobacteria* and *Firmicutes* produce DNA-damaging toxins. *C. trachomatis* infection, *BRCA* mutations, and microbiota contribute to progression/metastasis |
| Periodontal disease[98-100,103,104] | *Porphyromonas gingivalis* and *Fusobacterium nucleatum* are found in both periodontal and vaginal microbiota. Vaginal dysbiosis may trigger systemic inflammation that exacerbates gum disease and periodontitis progression |

Abbreviations: BV: Bacterial vaginosis; HPV: Human papillomavirus; IL-1β: Interleukin 1 beta; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; OAB: Overactive bladder; POP: Pelvic organ prolapse; SCFAs: Short-chain fatty acids; TNF-α: Tumor necrosis factor alpha; UI: Urinary incontinence.

(ii) Shared bacterial composition: Although oral and genital microbes originate from different environments, they share certain common pathogens. Bacteria such as *P. gingivalis* and *F. nucleatum*, associated with periodontal disease, can also be found in the microbiota of the female genital tract, suggesting an interaction between both microbiota.[99]
(iii) Impact of estrogens: Estrogens not only regulate the genital microbiota, but their decline also affects bone formation capacity.[102]

### 11.2. Clinical implications and management

The comprehensive management of postmenopausal women's health should consider both periodontal and vaginal health. Key recommendations include:
(i) Hormonal treatment: HRT may help restore estrogen levels, potentially improving both vaginal health and reducing the risk of periodontal disease.
(ii) Proper oral hygiene: It is essential to maintain rigorous oral hygiene, including regular brushing, flossing, and periodic visits to the dentist.
(iii) Probiotic supplements: Probiotics, especially those containing *Lactobacillus*, may be beneficial for balancing both vaginal and oral microbiota, reducing menopause-associated symptoms, and preventing periodontal disease.
(iv) Regular monitoring: Postmenopausal women should undergo regular gynecological and periodontal check-ups to detect and treat any signs of vaginal infection or periodontal disease early.

Menopause induces physiological changes that affect both the genital microbiota and periodontal health. The decrease in estrogens and the resulting systemic inflammation contribute to conditions like BV and periodontal disease, opening new possibilities for their preventive and therapeutic management. Table 1 provides an overview of the principal pathologies associated with menopause and microbiota alteration. These conditions include rUTIs, BV, PID, GSM, pelvic floor disorders, gynecological cancers (cervical, endometrial, and ovarian), and periodontal disease. All of these have been linked to shifts in microbial composition and function, which may contribute to their onset and progression.

## 12. Conclusion

The intestinal, urinary, and vaginal microbiomes form an interconnected ecosystem whose alteration during menopause, primarily caused by estrogen deficiency, is associated with various gynecological and urological disorders. Vaginal dysbiosis clinically manifested as dryness, atrophy, and urinary symptoms, significantly affects women's quality of life. Its management with local estrogens and probiotics has shown consistent benefits. Microbiota imbalance also influences urological health, and its modulation could serve as a promising tool against UTIs and pelvic floor dysfunctions, although further evidence is needed to confirm its effectiveness. Moreover, the VM appears to play a role in the progression of gynecological cancers such as cervical, endometrial, and potentially ovarian cancer, through mechanisms involving persistent HPV infection and the presence of bacteria associated with BV, opening the possibility for preventive strategies based on microbiome modulation.

This study's strengths include its narrative review design, which incorporates a rigorous selection of relevant, low-bias studies supported by current evidence from recognized databases, thereby reinforcing the clinical conclusions on postmenopausal microbiota. However, the narrative approach does not apply systematic quality criteria or a reproducible search strategy. In addition, the heterogeneity of the included studies and the lack of randomized controlled trials limit the ability to establish definitive causal relationships in all cases.

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