

# Probiotics in the Prevention and Treatment of Postmenopausal Vaginal Infections: Review Article

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Bacterial vaginosis (BV) and complicated vulvovaginal candidiasis (VVC) are frequently occurring vaginal infections in postmenopausal women, caused by an imbalance in vaginal microflora. Postmenopausal women suffer from decreased ovarian hormones estrogen and progesterone. A normal, healthy vaginal microflora mainly comprises *Lactobacillus* species (spp.), which act beneficially as a bacterial barrier in the vagina, interfering with uropathogens. During premenopausal period, estrogen promotes vaginal colonization by lactobacilli that metabolizing glycogen and producing lactic acid, and maintains intravaginal health by lowering the intravaginal pH level. A lower vaginal pH inhibits uropathogen growth, preventing vaginal infections. Decreased estrogen secretion in postmenopausal women depletes lactobacilli and increases intravaginal pH, resulting in increased vaginal colonization by harmful microorganisms (e.g., *Enterobacter*, *Escherichia coli*, *Candida*, and *Gardnerella*). Probiotics positively effects on vaginal microflora composition by promoting the proliferation of beneficial microorganisms, alters the intravaginal microbiota composition, prevents vaginal infections in postmenopausal. Probiotics also reduce the symptoms of vaginal infections (e.g., vaginal discharge, odor, etc.), and are thus helpful for the treatment and prevention of BV and VVC. In this review article, we provide information on the intravaginal mechanism of postmenopausal vaginal infections, and describes the effectiveness of probiotics in the treatment and prevention of BV and VVC. (**J Menopausal Med 2017;23:139-145**)

**Key Words:** Candidiasis, vulvovaginal · Postmenopause · Probiotics · Vaginal diseases · Vaginosis, bacterial

## Introduction

Demand for health functional foods are increasing as Korea is rapidly moving toward an aging society.<sup>1</sup> Especially, increase in elderly women due to prolonged lifespan in women promotes interest in postmenopausal health.<sup>2</sup> Postmenopausal women often complain of vaginal infections as well as genital and sexual symptoms, and climacteric syndromes such as hot flushes, insomnia, depression.<sup>3</sup> Bacterial vaginosis (BV) and complicated vulvovaginal candidiasis (VVC) are common postmenopausal vaginal infections. These vaginal infections can be ranged from superficial skin infec-

tions to life-threatening, thus prompt diagnosis and treatment are required.<sup>4</sup> If not treated promptly, in the worst cases, they can cause pelvic inflammation, endometriosis, chronic vaginitis, and infertility; furthermore, recurrence after treatment is common. Postmenopausal vaginal infections including BV and VVC are caused by changes in the intravaginal environment, which are closely related to imbalances in vaginal microflora composition due to decreased estrogen.

Pathogenic microorganisms including bacteria, archaea, protists, fungi, and viruses exist within the environment of the vaginal microflora. The vaginal microflora is composed

Received: September 8, 2017 Revised: October 19, 2017 Accepted: October 21, 2017

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of a mixture of bacteria including both gram-negative and gram-positive bacteria, and an imbalance in the composition of the microflora causes infections and diseases in the vagina.<sup>5,6</sup> The vaginal microflora play an important role in protecting against pathogens and maintaining vaginal health, thus preventing vaginal diseases, such as BV and VVC, and their recurrence. These vaginal infections are especially prevalent in postmenopausal women who experience an imbalance in the vaginal microflora caused by decreased or absent estrogen.

Variety of method (e.g., phytoestrogen, herbal therapies, plant extracts, and exercise) have been investigated for relieving postmenopausal symptoms and improving vaginal health.<sup>3,7</sup> Probiotics products are verified its efficacy on improving vaginal health by maintaining the normal vaginal lactobacilli microbiota.<sup>5</sup> Probiotics are living microorganisms that act beneficially in the vagina as a bacterial barrier, interfering with uropathogens. Probiotics suppress vaginal colonization by harmful microorganisms such as *Gardnerella vaginalis* (*G. vaginalis*), *Escherichia coli* (*E. coli*), and *Candida*, thus maintaining vaginal health. The vaginal microflora in patients with vaginal infections such as BV and VVC contains a reduced number of lactobacilli compared to healthy populations. Hence, lactobacilli are the most common microorganisms used as probiotics.

Fluconazole, metronidazole, and clindamycin have generally been used as antimicrobials in the treatment of BV and VVC; however, long-term antibiotic administration is associated with high rates of recurrence (approximately 50%).<sup>8</sup> Therefore, the therapeutic use of probiotics has been introduced as a new strategy for the treatment and prevention of postmenopausal vaginal infections. Herein, we review the use of probiotics in the treatment of postmenopausal BV and VVC, describing the mechanisms of lactobacilli and vaginal flora. We also describe the effectiveness of probiotics in the treatment and prevention of postmenopausal vaginal infections such as BV and VVC.

## Vaginal Infections from the Premenopausal to the Postmenopausal Period

Vaginitis and vaginosis are defined as separate vaginal conditions. The important characteristic of the former condition is inflammation, whereas the latter reflects abnormal changes in the vaginal ecosystem due to reduced concentrations of dominant lactic acid-producing *Lactobacillus* spp. and excessive growth of aerobic or anaerobic bacteria that are normally found in the vagina. When premenopausal woman complain of vaginal symptoms such as itching and smelly vaginal discharge, a differential diagnosis among the three most common types of vaginitis, namely BV, trichomoniasis, and vaginal candidiasis, is needed. Among these three diseases, BV is the most prevalent (40–50%), followed by vaginal candidiasis (20–25%) and trichomoniasis (15–20%).<sup>9</sup> Although itching and irritation are symptoms of vaginal candidiasis, and foul odor indicates BV, pruritus of the vagina is typically found in fewer than 50% of women with VVC.<sup>10</sup>

The vaginal environment is sterile until puberty, and is colonized by lactobacilli due to hormonal changes after puberty.<sup>11</sup> Decreased estrogen and progesterone in postmenopausal women make vaginal tissues thinner and less elastic. These vaginal atrophic changes affect up to 47% of postmenopausal women.<sup>12</sup> Furthermore, 56% of women with menopausal symptoms have abnormal vaginal flora other than lactobacilli-dominant conditions.<sup>13</sup> Endocrine changes in postmenopausal women lead to changes in vaginal pH, cellular glycogen content, and vaginal microflora, all of which play roles in vulvovaginal symptoms such as vaginal infections.<sup>14</sup> Increased populations of *G. vaginalis* and gram-negative bacteria are more frequently detected in postmenopausal women.<sup>15,16</sup> Patients with vaginal infections report a number of vaginal complaints, such as vulvovaginal pruritus, vaginal pain, irritation, soreness, dyspareunia, burning on micturition, and a whitish, cheesy vaginal discharge. However, because BV infection is asymptomatic and non-specific in up to 50% of women, the reported prevalence of BV varies from 6% to 50%.<sup>17</sup> If vaginal infections such as BV and VVC are not diagnosed and treated promptly, symptoms may worsen, leading to pelvic inflammation, endometriosis,

and other serious conditions.

### 1. BV in the premenopausal and postmenopausal period

Vaginitis frequently occurs after reproductive age; the three main types are BV, *Trichomonas vaginalis* vaginitis, and fungal vaginitis. Among these, BV is the most common, constituting 40% to 50% of all cases of vaginitis. BV usually occurs in vaginal environments of an increase in the intravaginal pH to >4.5. *G. vaginalis* is the most frequently detected BV-causing bacterium, along with *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Mobiluncus* spp., *Fusobacterium* spp., and *Atopobium vaginae*.<sup>18</sup> Increased *G. vaginalis* in the vaginal microflora is associated with frequent sexual intercourse, risky sexual practices, frequent use of vaginal douches, and other related behaviors. In these conditions, intravaginal epithelial cells are flattened, and beneficial bacteria such as lactobacilli are decreased or absent, whereas BV-causative bacteria are increased, thus leading to BV. Thus, BV exhibits a decreased concentration of lactobacilli and overproliferation of microorganisms such as *G. vaginalis* and other anaerobes. BV caused by pathogenic anaerobic bacteria is most prevalent in younger women, it spontaneously regresses in up to 50% of premenopausal women.<sup>19</sup> BV is an important common cause of vaginitis, pelvic inflammatory disease, and various sexually transmitted diseases.<sup>20,21</sup>

Microscopic examination of vaginal samples is the most useful diagnostic tool, easily detecting *Candida* hyphae, motile *Trichomonas* with flagellae, clue cells indicative of BV, and a lack of lactobacilli. BV is clinically diagnosed by the Amsel criteria, which require at least three positive findings of the four diagnostic criteria: a fishy odor after a 10% potassium hydroxide test for vaginal secretion, the presence of non-inflammatory vaginal discharge, clue cells on microscopic examination, and vaginal fluid pH >4.5.<sup>20</sup> Diagnosis of BV for research purposes is usually based on the Nugent criteria.<sup>22</sup>

Antibiotic therapy (e.g., clindamycin and metronidazole) has generally been used for the management of BV. Antibiotic use alters the abnormal vaginal microflora, inhibits anaerobes that support *G. vaginalis*, as well as some other

anaerobes, without affecting lactobacilli, thereby treating BV and preventing its recurrence. However, antibiotic use causes side effects such as nausea, dizziness, rash, thrush, as well as antibiotic resistance and recurrence. Lactobacilli probiotics have been developed to effectively treat and prevent BV without antibiotic resistance or adverse effects even with long-term use. Recently, probiotics used in conjunction with antibiotics has been proposed as a new remedy for vaginal infections including BV.

### 2. VVC

VVC is the second-most frequent vaginal infection, experienced by 75% of fertile women more than once in their lifetime. VVC is an infection mainly caused by *Candida* spp. that affects 70% to 75% of women, among whom 40% to 50% experience recurrence of VVC. The prevalence of VVC is 20% to 30% among reproductive-aged women, increasing in women aged 20 to 29, and peaking in the third decade of life. The prevalence of VVC in Korea has not been reported, but Health Insurance Review Agency data showed the highest incidence of VVC among Korean women in age group of 30 to 39 years (294,888 cases in 2016, diagnosis code B37). The VVC incidence decreases to 6% to 7% in postmenopausal women.<sup>23</sup> These data also showed trend of increased incidence of VVC (790,823 cases to 1,028,709 cases in all aged women) and increased socioeconomic burden (24,401,467,000 won to 46,822,175,000 won in all aged women and men) from 2012 to 2016.

Many VVC patients are women of childbearing age, menopausal women who use exogenous estrogen, or immunocompromised women. Although the direct causes of VVC have not been identified, diabetes mellitus, continuous antibiotic administration, increased estrogen levels, and immunocompromised status are suggested have been the main correlates of VVC.<sup>24</sup> Representative symptoms of VVC are dysuria, edema, inflammation, pruritus, and cheese-like vaginal discharges.<sup>25</sup>

Although 100 to 200 species of *Candida* are potentially causative organisms of VVC, over 85% of patients present with VVC due to *Candida albicans* (*C. albicans*).<sup>26</sup> Uncomplicated VVC, mainly caused by *C. albicans*, is characterized by mild to moderate levels of infection that is responsive to all antifungal therapies, and it is generally observed in non-

pregnant women. Short-term administration of antibacterial cream and vaginal tablets (e.g., butoconazole, clotrimazole, or miconazole), which are mainly used in the early phases of uncomplicated VVC, is effective in approximately 90% of patients.<sup>27,28</sup> In contrast, complicated VVC involves severe levels of chronic or recurrent VVC caused by non-*C. albicans* candidiasis. This condition occurs in abnormal hosts such as patients with uncontrolled diabetes, debilitation, or immunosuppression. Postmenopausal women with these diseases and those who are taking medications or hormone replacement therapy are particularly at risk of complicated VVC.<sup>29</sup>

Interestingly, BV and VVC occur under different vaginal conditions. VVC occurs at lower vaginal pH conditions (<4.5) that are common in premenopausal women.<sup>30</sup> For this reason, VVC is expected to be less prevalent among postmenopausal vaginal conditions, with reduced glycogen and higher vaginal pH >5.0.<sup>17</sup> In contrast, BV occurs under more alkaline vaginal conditions (pH >4.5) due to colonization by anaerobic bacteria and fewer lactobacilli, conditions frequently observed in postmenopausal women.<sup>30,31</sup>

## Antibiotics and Probiotic Therapies for BV and VVC

Fluconazole, metronidazole, and clindamycin have been commonly used as antibiotics for treatment of vaginal infections such as VVC and BV. Although these antibiotics suppress the activation of intravaginal bacteria and anaerobes causing vaginal infections, their use is problematic due to antibiotic resistance, adverse effects, and recurrences. In the case of metronidazole or clindamycin, initial cure rates in the treatment of BV were poor, in the range of 10% to 15%, and BV recurrence rates were as high as 80% among patients who showed an initial response.<sup>32</sup> Long-term or repeated antibiotic exposure causes antibiotic resistance and the persistence of BV-inducing microorganisms, thus causing high rates of recurrence. Therefore, lactobacilli probiotics have recently been gradually replacing antibiotic therapy for the treatment and prevention of vaginal infections such as BV and VVC.

Probiotics are defined as 'live microorganisms which when administered in adequate amounts confer a health benefit

on the host'.<sup>33</sup> The beneficial effects of probiotics have been well-known include bowel disorders (e.g., intestinal health, lactose metabolism, diarrhea diseases), coronary heart disease, allergy, and cancer prevention.<sup>34</sup> Regarding vaginal health, probiotics improve the therapeutic outcome in women with vaginal infections by maintaining the normal vaginal lactobacilli microbiota. It produces lactic acid and lowers the intravaginal pH level of 3.5 to 4.5.<sup>5</sup> As a result, it play a key role in maintaining vaginal environment more protective from harmful microorganisms. Probiotics indirectly contribute to treatment of BV and VVC, preventing the infections' recurrence and contagion. Many studies have confirmed that probiotics are effective in the treatment of vaginal infections such as BV and VVC by positively altering the intravaginal microbiota composition.<sup>5</sup> Representative species of probiotics include *Lactobacillus*, *Lactococcus*, *Enterococcus*, *Streptococcus*, and *Bifidobacterium*. The best-known intravaginal beneficial probiotic species are in the *Lactobacillus* genus. *Lactobacillus* spp. decompose carbohydrates and maintain an acidic intravaginal microflora by generating lactic acid and CO<sub>2</sub>, thus preventing vaginal colonization by harmful microorganisms such as *Enterobacteria*, *E. coli*, *Candida*, and *G. vaginalis*, and preventing their growth.<sup>35</sup> However, an imbalance between Gram-negative organisms (e.g., *Candida*, *G. vaginalis*) and Gram-positive bacteria (e.g., *Lactobacillus* spp.) in the vaginal microbiota is seen in vaginal infections such as BV and VVC. Beneficial Gram-positive bacteria, i.e., lactobacilli, are suppressed, while Gram-negative bacteria colonize the intravaginal microflora, leading to vaginal infections. Hormonal changes in the postmenopausal period influence changes in the intravaginal microflora. Postmenopausal women with decreased estrogen have reduced levels of intravaginal lactobacilli; thus, their intravaginal microflora can be colonized by harmful microorganisms that cause BV and VVC.

The efficacy of probiotics in BV treatment was demonstrated in a clinical trial.<sup>36</sup> In the probiotics intervention group (IG), 51.1% had a normal vaginal microbiota composition of *G. vaginalis*, fungi, mixed flora, *Trichomonas*, mycosis, and lactobacilli after taking probiotics, whereas a normal composition was reported in only one-fifth (20.8%) of the control group (CG) treated with a placebo. Regarding BV recurrence, the incidence of *G. vaginalis* was signifi-

cantly lower in the IG than in the CG, whereas *G. vaginalis* in the CG increased over time. BV symptoms were also decreased in the IG.<sup>37</sup>

Studies have also shown the efficacy of probiotics combined with antibiotics in treating BV. Long-term antibiotic administration for BV was associated with adverse effects, including a high probability of BV recurrence due to antibiotic resistance derived from repeated exposure to antibiotics, whereas short-term administration combining antibiotics with probiotics decreased the number of harmful intravaginal microorganisms. This means that co-treatment with probiotics and antibiotics was more effective in BV treatment and recurrence prevention than was antibiotic administration alone.<sup>38,39</sup>

In the case of VVC, complicated VVC, which frequently occurs in postmenopausal women, requires a longer course of treatment than does uncomplicated VVC. Using antimicrobials in patients with complicated VVC is not as effective as it is in uncomplicated VVC due to antimicrobial resistance.<sup>40</sup> The efficacy of oral or vaginal *Lactobacillus* strains in the treatment of complicated VVC has been demonstrated in many studies, and it also lowers the possibility of recurrence. In Davar et al.'s study,<sup>41</sup> 7.2% of probiotic and 35.5% of placebo groups presented with a recurrence of complicated VVC within 6 months. De Seta et al.<sup>42</sup> evaluated the effect of probiotics combined with antifungal medication on VVC treatment. The results showed a significant increase in lactobacilli and improved vaginal discomfort in the IG treated with probiotics followed by antifungal medication.

As Korean studies on *Lactobacillus* spp. obtained from Korea women, Chang et al.<sup>43</sup> reported that among 10 isolates selected from the vagina of Korean women, *Lactobacillus crispatus* (*L. crispatus*) KLB 46 showed the most promising antimicrobial activity. Oh and Cho<sup>44</sup> also reported that *L. crispatus* was the most frequently detected *Lactobacillus* from healthy Korean women in age of twenties. Because *L. crispatus* KLB 46 is the most prevalent *Lactobacillus* spp. in healthy Korean women and has strong antimicrobial activity against pathologic organisms, it can be a good candidate for probiotic treatment for BV and VVC in Korean women.

## Conclusion

BV and VVC are the most prevalent vaginal infections, and many women experience them more than once in their lifetimes. These vaginal infections are likely to occur in women with immunosuppression or uncontrolled diabetes mellitus, and in postmenopausal women. Postmenopausal women commonly experience decreased estrogen secretion, resulting in a depletion of lactobacilli and an imbalance in vaginal microflora, accompanied by increased vaginal colonization by *G. vaginalis* and *Candida*, the main causes of BV and VVC. Although these vaginal infections are generally treated with antibiotics, repeated exposure to antibiotics is associated with a high probability of complications, recurrence, and antibiotic resistance. The use of probiotics alone or in combination with antimicrobials positively alters the vaginal microflora and prevents vaginal infections in postmenopausal women with absent or decreased estrogen. Further studies on the action of probiotics on changes in the vaginal microbiota are required.

## Acknowledgement

This research was supported by High Value-added Food Technology development program, Ministry of agriculture, Food and Rural Affairs, Republic of Korea (116022-03-2-HD040).

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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