Effects of Probiotics on the Recurrence of Bacterial Vaginosis: A Review

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Abstract

Objective. Bacterial vaginosis (BV) is a common cause of genital discomfort in women in reproductive ages, which causes many complications. Bacterial vaginosis is usually treated by metronidazole and clindamycin. However, this protocol does not prevent its recurrence, which is a main complaint of the patients. The number of lactobacilli in the vagina of women with BV is significantly lower than that in healthy women. Hence, efforts have been made to normalize vaginal flora by oral or vaginal administration of lactobacilli. The objective of the present study was to review clinical evidences available regarding the efficacy of probiotics in the prevention and treatment of BV.

Materials and Methods. Published randomized controlled trials were searched in PubMed, Science Direct, and the Cochrane Database between 1990 and 2011. Search terms included bacterial vaginosis, urinary tract infection, lactobacillus, and probiotics.

Results. Orally consumed probiotics are believed to ascend to the vaginal tract after they are excreted from the rectum; vaginal administration allows for direct replacement of the probiotics for unhealthy vaginal microbiota and occupation of specific adhesion sites at the epithelial surface of the urinary tract, which consequently results in maintenance of a low pH and production of antimicrobial substances like acids and hydrogen peroxide. Receiving Lactobacillus acidophilus, Lactobacillus rhamnosus GR-1, and Lactobacillus fermentum RC-14 at a dose of at least 10^8 CFU/day for 2 months has been shown to present the patients with better results.

Conclusions. Although the results of different studies are controversial, most studies have been in favor of the probiotics in the prevention or treatment of BV, and no adverse effects have been reported. Therefore, it may be helpful to recommend daily consumption of probiotic products to improve public health among women.

Key Words: probiotics, bacterial vaginosis, urinary tract infection

Bacterial vaginosis (BV) is a syndrome characterized by a change in vaginal ecology, where the normal flora of Lactobacillus morphotypes is replaced by a mixed microbial flora consisting of anaerobes and Gardnerella vaginalis, and an increase in the vaginal pH over 4.5; it often originates as a result of a reduction in, or in the absence of, Lactobacillus colonization and overgrowth of several facultative and obligate anaerobic bacteria [1, 2]. Bacterial vaginosis is considered as the most common form of vaginal infection among women of reproductive age affecting about 19% to 24% of them [3]. The prevalence of BV varies in different parts of the world; it is higher in developing countries. Moreover, 10% to 26% of pregnant women in the United States have been reported to suffer from BV. The disease has been found in 12% to 25% of
women in routine clinic populations [4]. A clinical manifestation of BV is irritating malodorous vaginal discharge, especially a fishy odor, which is sometimes stronger after a woman had sex. Burning or discomfort during urination is a symptom of BV [5, 6]. Clinical studies have demonstrated an association between BV with adverse pregnancy outcomes [7], such as premature rupture of membranes, preterm birth [8], and postpartum endometritis. Women with upper genital tract infections such as pelvic inflammatory disease, endometritis, postgynecologic surgery infections, and cervicitis [9, 10] are more susceptible to having babies of low birth weight [11–13]. It has also been suggested that the presence of BV increases the risk for human immunodeficiency virus infection [14–16]. It is noteworthy that many women with BV do not show any symptoms [17].

What patients with BV and their caregivers are mostly looking for is a treatment protocol to get them rid of the recurrence of the infection. Several methods have been offered for the treatment of BV. Either oral or vaginal metronidazole or vaginal clindamycin [18] provides equivalent treatment for BV in nonpregnant women. Oral clindamycin 300 mg twice daily for 7 days is an effective treatment. There is conflicting evidence regarding the efficacy of a single 2-g dose of oral metronidazole [19, 20]. As many as 30% of women relapse within 1 month of treatment and it is more common among women treated with topical compared with those treated with systemic antibiotics [21, 22]. Another alternative for the treatment of BV is the use of probiotics—live microorganisms that, when consumed in appropriate amounts, confer a health benefit on the host [23]. When ingested, some of these probiotic microorganisms are able to resist the physicochemical conditions prevailing in the digestive tract [16, 24–26]. The term “probiotic” is an etymological hybrid derived from Greek and Latin meaning “for life” [25]. Traditionally, yogurt was the first food to which probiotics were added. Recently, development of novel probiotic foods has attracted great attention, and manufacturers are coming out with new products including ice cream, cheese, chocolate, beverages, cereals, and vegetable products. Different forms of probiotic supplements are also available in the market today, including pills, capsules, tablets, gel caps, liquids, and powders [27]. Both foods and supplements have been used as carriers for probiotics in clinical trials investigating the health benefits of probiotics. Some mostly documented health effects of probiotics are relief of diarrhea, improvement in lactose intolerance, relief of respiratory and urinary tract infections, and immunomodulatory, anticarcinogenic, antidiabetic, hypocholesterolemic, and hypotensive properties [28–30]. By reducing inflammatory responses, probiotics have been shown to correct insulin sensitivity and reduce development of diabetes mellitus [28, 31]. A beneficial effect of “lactic acid–producing” microorganisms on vaginal microbiota has also been suggested about 100 years ago [23, 32].

**MATERIALS AND METHODS**

To review the available evidence on the efficacy of probiotics in the prevention and treatment of BV, randomized controlled trials were searched in PubMed, Science Direct, and Cochrane Database between 1990 and 2011. The search terms included *probiotics, Lactobacillus, bacterial vaginosis*, and *urinary tract infections*.

**Application of Probiotics in BV Treatment**

There are important issues to which great attention must be paid regarding the effects of probiotics on BV treatment and prevention. The basis for use of probiotics in BV treatment was developed in 1973, when healthy women with no history of urinary tract infection were reported to have lactobacilli in their vagina [17]. *Lactobacillus* organisms that predominate in the vagina of healthy women spread from their rectum and perineum and form a barrier to the entry of uropathogens from the vagina into the bladder [33]. Similar to pathogenic bacteria with colonic origin, which cause urogenital disorders, probiotic bacteria must be capable of ascending to the vaginal tract after passing out from the rectum. This application is also justified by observations that the normal vaginal microbiota colonizes from an intestinal origin, which means that microbial ascension is a natural process actually contributing to the development of a healthy vaginal microbiota in the host [34]; this has been shown by a number of clinical trials as well [35]. Probiotics are believed to protect the host against infections by means of several mechanisms including the following: (1) occupation of specific adhesion sites at the epithelial surface of the urinary tract; (2) maintenance of a low pH and production of antimicrobial substances like acids, hydrogen peroxide, and bacteriocins; (3) degradation of polyamines; and (4) the production of surfactants with antiadhesive properties [36, 37]. Probiotics have been administered both orally and vaginally; however, it is still not clear as to which route is more efficient. Foods and supplements have been used as carriers when oral administration was aimed; no studies have compared the efficacy of these 2 methods. Not all strains have exerted the desired effects in the patients; poor...
colonization of some strains in the vagina could be a reason [34, 38, 39]. The most profitable dose and treatment duration must be taken into consideration as well. Figure 1 summarizes the process through which a healthy woman is infected with BV and how probiotics may provide protection against this disease (Figure 1).

Clinical Trials of Probiotics in the Treatment or Prevention of BV
Probiotics have been administered through 2 routes in attempt to prevent BV: vaginal and oral. In studies that use vaginal form, probiotics must colonize the vagina to confer the benefits claimed for them. Therefore, they have to reach the organ intact. Vaginal probiotic capsules and cream have widely been used, by means of which, the probiotic bacteria are directly introduced into the vagina [40]. Oral method, on the other hand, has been introduced in an attempt to come up with a more practical route that could also prevent BV in healthy women as well as present the consumer with other health benefits of these beneficial microorganisms [39, 41]. A study by Marcone et al. [42] indicated that oral capsules containing a variety of probiotic bacteria including Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at a dose of $2.5 \times 10^9$ CFU for 14 days after metronidazole therapy reduced the Nugent score in 3 subjects of the intervention group, while no improvement was observed in subjects of the control group. A similar study by Anukam et al. [36] showed that, after oral administration of capsules containing either $1.0 \times 10^9$ CFU of L. rhamnosus GR-1 and L. reuteri RC- for 7 days, BV cure rate was $88\%$ in probiotic group versus $40\%$ in the placebo group. In the same way, Neri et al. [43] confirmed that an amount of $10^9$ CFU of L. rhamnosus GR-1 and Lactobacillus fermentum RC-14 in skim milk for 14 days correlated with a healthy vaginal flora in up to $90\%$ of patients. Shalev et al. [44] showed that, after weeks of intervention with $1.0 \times 10^8$ CFU of Lactobacillus acidophilus in yogurt, reduction in BV episodes at 1 month was $60\%$ for probiotic yogurt versus $25\%$ for conventional yogurt. It was also noted that vaginal douche with yogurt containing L. acidophilus for 7 days increased the percentage of BV cure rate to $88\%$ in the probiotic group at 4 and 8 weeks versus $38\%$ in the control group [43]. Amounts of $10^8$ CFU of L. rhamnosus, L. acidophilus, and Streptococcus thermophilus for 21 days were associated with lower recurrence rates for BV in women who received probiotic prophylaxis [45]. Vaginal tampons containing $10^8$ CFU of Lactobacillus gasseri, Lactobacillus casei, L. rhamnosus, and L. fermentum increased microbiological cure observed based on the Nugent score and Amsel criteria [46]. Patients with BV, when given more than $4 \times 10^4$ CFU of L. rhamnosus in a vaginal tablet, showed significant improvement in comparison to the control group at Day 90 [42]. The vaginal flora was enhanced significantly by vaginal tablets with more than $10^7$ CFU of L. acidophilus for 6 days [47]. Vaginal capsules containing between $10^8$ and $10^{10}$ CFU of L. gasseri LN40, L. fermentum LN99, L. casei subsp. rhamnosus LN113, and Propionibacterium acidilactici LN23 for 5 days had a good colonization rate in the vagina of patients with BV, and women receiving the probiotics were cured 2 to 3 days after administration [48].

As for administration route, no studies by now have investigated the efficacy of foods versus supplements in exerting the benefits expected from the probiotics. Probiotics have been shown to exert the beneficial effects both in foods, such as yogurt [49] and ice cream, and in supplements [30]. Supplements have been used in a greater number of studies in patients with BV and the number of studies in which foods were opted as probiotic vehicles is limited. Consumption of fermented milk containing lactobacilli has been found to reduce BV episodes [44]. Supplements have been used in a variety of forms including oral capsules, vaginal tablets, and vaginal capsules. Clinical trials in which patients were administered oral capsules reported a positive effect of the treatment on BV [19, 33, 39, 50, 51]. Vaginal probiotic tablets were reported to be effective in alleviating BV symptoms and decreasing its recurrence [4, 32, 42, 52–56]. Some studies [19, 52, 57–60] have also reported that vaginal capsules are capable to efficiently ease BV symptoms. Various in vitro studies have shown that specific strains of lactobacilli inhibit the growth of bacteria causing BV by producing H$_2$O$_2$, lactic acid, and/or bacteriocins and/or inhibit the adherence of G. vaginalis to the vaginal epithelium [52, 61, 62]. According to a general theory, a probiotic must have 2 criteria to be selected as an efficient strain in the treatment of urogenital infections: 1) it must be able to colonize the host without any adverse side effects and 2) it must be capable of inhibiting urogenital pathogens [65]. According to Reid and Bruce [39], different probiotic bacteria have varying capabilities to colonize the vagina of different patients; this indicates the importance of using a combination of strains in probiotic products [33, 64]. Oral administration of L. acidophilus, or intravaginal administration of L. acidophilus or L. rhamnosus GR-1 and L. fermentum
RC-14, has been documented to most efficiently increase the numbers of vaginal lactobacilli, restore the vaginal microbiota to normal, and to cure women with BV [52].

Researchers have tried different dosages in their attempts to treat BV with probiotics, many of which have resulted in positive outcomes. There is strong evidence that BV is most appropriately treated when more than $10^8$ viable organisms per day are used [25, 65]. However, the minimum dose that can generally confer the favored benefits in women must be determined.

A major concern regarding BV is that the patients usually complain of the recurrences of the disease. Thus,

### Table 1. Effects of Administration of Probiotics on BV (Performed Between 1990 and 2011)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Health condition</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral yoghurt containing $1.0 \times 10^5$ CFU of L. acidophilus, once daily for 2 mo</td>
<td>Bacterial vaginosis, candidiasis</td>
<td>Reduction in BV episodes at 1 mo vs 25% for pasteurized</td>
<td>Shalev et al. [44]</td>
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<tr>
<td>Oral capsules containing $10^5$ CFU of L. rhamnosus GR-1 plus L. fermentum RC-14 or L. rhamnosus, each day for 28 d</td>
<td>Bacterial vaginosis</td>
<td>Normal vaginal flora was restored using specific probiotic strains administrated orally</td>
<td>Reid et al. [17]</td>
</tr>
<tr>
<td>Skim milk containing $10^5$ CFU of L. rhamnosus GR-1 and L. fermentum RC-14, twice daily for 14 d</td>
<td>Vaginal</td>
<td>Treatment correlated with a healthy vaginal flora in up to 90% of patients</td>
<td>Gardiner et al. [66]</td>
</tr>
<tr>
<td>Oral capsule containing $8 \times 10^4$ CFU of 1- L. rhamnosus GR-1/L. fermentum RC-14 and $6 \times 10^4$ CFU L. rhamnosus GR-1/L. fermentum RC-14 3-L. rhamnosus GR-1/L. fermentum RC-14, daily for 28 d</td>
<td>History of BV</td>
<td>Through 6 wk after treatment with probiotics, Nugent score decreased, indicative of BV resolution</td>
<td>Anukam et al. [36]</td>
</tr>
<tr>
<td>Oral capsules containing $10^4$ CFU of L. rhamnosus GR-1 and L. fermentum RC-14, once daily for 60 d</td>
<td>Bacterial vaginosis</td>
<td>Probiotics colonized the vagina properly and the Nugent score normalized after the treatment</td>
<td>Reid et al. [68]</td>
</tr>
<tr>
<td>Oral capsules containing $10^2$ CFU of L. reuteri RC-14, L. rhamnosus GR-1, twice daily from Days 1 to 30</td>
<td>Vaginal infections</td>
<td>Lactobacilli counts increased while yeast and coliforms decreased significantly after supplementation</td>
<td>Reider et al. [34]</td>
</tr>
<tr>
<td>Oral capsules containing $2.5 \times 10^7$ CFU of L. rhamnosus GR-1 and L. reuteri RC-14, 14 d</td>
<td>Bacterial vaginosis</td>
<td>The median difference in Nugent scores between baseline and the end of the study was 3 in the intervention group and 0 in the control group</td>
<td>Petrićević et al. [57]</td>
</tr>
<tr>
<td>Vaginal tablets containing $10^4$ CFU of L. acidophilus and estriol 0.03 mg, once daily or twice daily for 6 d</td>
<td>Bacterial vaginosis</td>
<td>Microbiological cure (Nugent criteria) and clinical cure were observed on Days 15 and 28 after intervention</td>
<td>Parent et al. [4]</td>
</tr>
<tr>
<td>Vaginal tampons containing $10^5$ CFU of L. gasseri, L. casei var rhamnosus, and L. fermentum, 5 tampons during menstruation</td>
<td>Bacterial vaginosis</td>
<td>Microbiological cure was observed based on Nugent score and Amsel criteria</td>
<td>Eriksson et al. [46]</td>
</tr>
<tr>
<td>Vaginal tablet containing $&gt;10^5$ CFU of L. acidophilus, 0.03 mg of estriol and 600 mg of lactose, daily for 6 d</td>
<td>Vaginal infections</td>
<td>Vaginal flora was enhanced significantly by the probiotic administration in combination with low-dose estriol</td>
<td>Oszkinay et al. [47]</td>
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<tr>
<td>Vaginal tablet containing $&gt;4 \times 10^4$ CFU of L. rhamnosus, once a week at bedtime for 2 mo</td>
<td>Bacterial vaginosis</td>
<td>Significant difference between the 2 treatment groups were seen at Day 90</td>
<td>Marcone et al. [42]</td>
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<tr>
<td>Vaginal tablets containing $10^5$ CFU of L. brevis, L. salivarius subsp. salicinus, and L. plantarum, for 7 d</td>
<td>Bacterial vaginosis</td>
<td>All of the patients in the probiotic group were free of BV, showing a normal or intermediate vaginal flora</td>
<td>Mastromarino et al. [32]</td>
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<tr>
<td>Vaginal application containing $&gt;10^5$ CFU of L. rhamnosus, for 6 mo</td>
<td>Prevent the recurrence of bacterial vaginosis</td>
<td>The vaginal administration of the probiotic allows stabilization of the vaginal flora and reduces BV recurrence</td>
<td>Marcone et al. [52]</td>
</tr>
<tr>
<td>Vaginal capsules containing between $10^4$ and $10^5$ CFU of L. gasseri LN40, L. fermentum LN99, L. casei subsp. rhamnosus LN113, and P. acidilactici LN23, for 5 d, after conventional treatment of bacterial vaginosis</td>
<td>Bacterial vaginosis, vulvovaginal candidiasis</td>
<td>The vaginal flora of patients with BV and women receiving LN were cured 2-3 d after administration</td>
<td>Ehrström et al. [48]</td>
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<tr>
<td>Vaginal capsule containing $10^5$ CFU of L. rhamnosus, L. acidophilus, and S. thermophilus, 21 d, for 7 d on 7 d off, and 7 d on.</td>
<td>Prophylaxis bacterial vaginosis</td>
<td>Probiotic prophylaxis resulted in lower recurrence rates for BV women</td>
<td>Ya et al. [45]</td>
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</table>
seeking for treatments that prevent the recurrence of BV as well may be a priority. Probiotics are a good option to fulfill this goal, provided that they are properly colonized in the vagina. Parent et al. [4] found that cure was more common, and the number of vaginal lactobacilli was significantly higher, in women with BV at both 2 and 4 weeks after the start of a 6-day treatment with \textit{L. acidophilus} and estriol, when compared to women with BV who received a placebo. However, most clinical trials have reported that 2 months of oral administration of \textit{L. acidophilus}, \textit{L. rhamnosus} GR-1, and \textit{L. fermentum} RC-14 can be more effective in preventing recurrences of BV and/or increasing vaginal colonization with lactobacilli, thus restoring the normal vaginal microbiota [66] (Table 1).

**CONCLUSIONS**

\textit{Lactobacilli} strains are probiotic bacteria. Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts [69].

Results of studies of lactobacilli for the treatment of BV in women were inconclusive but promising. Various in vitro studies have shown that specific strains of lactobacilli inhibit the growth of bacteria causing BV by producing \( \text{H}_2\text{O}_2 \), lactic acid, and/or bacteriocins and/or inhibit the adherence of \textit{G. vaginalis} to the vaginal epithelium. Most relevant clinical trials have suggested that oral administration of \textit{L. acidophilus}, or intravaginal administration of \textit{L. acidophilus} or \textit{L. rhamnosus} GR-1 and \textit{L. fermentum} RC-14, is able to increase the numbers of vaginal lactobacilli, to restore the vaginal microbiota to normal, and to cure women of BV, although several trials demonstrated intravaginal instillation of lactobacilli had no significant effect on the treatment of BV. The dominance of lactobacilli in healthy vaginal microbiota and its obliteration in BV have given rise to the concept of oral or vaginal instillation of probiotic \textit{Lactobacillus} strains to restore the balance. Indeed, available evidence now indicates that certain strains of lactobacilli administered intravaginally are capable of colonizing the vagina.

This review confirms the influence of lactobacilli as an adjuvant to standard treatment with antibiotics, nonchemotherapeutic means to restore and maintain a normal urogenital flora, and shows that probiotic bacteria especially \textit{L. acidophilus}, \textit{L. rhamnosus} GR-1, and \textit{L. fermentum} RC-14 when administered over \( 10^{8} \) CFU for 2 months can most appropriately normalize the vaginal flora, help cure the existing infection, and prevent recurrence of BV. Longer periods of probiotic administration may be useful for long-term control of BV relapses after conventional therapy with metronidazole. Probiotics have been reported useful when used either vaginally or orally; foods and supplements have both been shown to be efficient vehicles as well. However, because BV is a common disorder for the prevention of which the vaginal flora needs to be normal and devoid of pathogens.
by the help of beneficial bacteria, suggesting women to consume probiotic foods will not only protect them against BV but will also reward them with other health benefits of probiotics.

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