Probiotics for the treatment of women with bacterial vaginosis

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ABSTRACT
This review considers whether probiotics are effective agents for the treatment and/or prevention of bacterial vaginosis (BV). There seems to be an association between the absence of, or low concentrations of, vaginal lactobacilli and the development of BV. Many studies have suggested that the presence of H₂O₂-producing vaginal lactobacilli may protect against BV, although some studies do not support this hypothesis. In-vitro studies have suggested that certain specific strains of lactobacilli are able to inhibit the adherence of Gardnerella vaginalis to the vaginal epithelium and/or produce H₂O₂, lactic acid and/or bacteriocins, which inhibit the growth of bacteria causing BV. Clinical trials showed that intra-vaginal administration of Lactobacillus acidophilus for 6–12 days, or oral administration of L. acidophilus or Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum RC-14 for 2 months, resulted in the cure of BV (defined as a 0–1 positive score according to Amsel’s criteria), and/or reduced the recurrences of BV, and/or caused an increase in vaginal lactobacilli and restoration of a normal vaginal microbiota, significantly more frequently than did a placebo, acetic acid or no treatment. However, several trials have found no significant difference in the cure rate of BV and in the number of vaginal lactobacilli after intra-vaginal instillation of lactobacilli when compared with the effect of a placebo or oestrogen. Thus, although the available results concerning the effectiveness of the administration of lactobacilli for the treatment of BV are mostly positive, it cannot yet be concluded definitively that probiotics are useful for this purpose.

Keywords Bacterial vaginosis, Gardnerella vaginalis, lactobacilli, probiotics, review, treatment, vaginosis

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INTRODUCTION
Bacterial vaginosis (BV) is a common vaginal infection causing significant gynaecological and obstetric morbidity. Apart from causing irritating symptoms, mainly a malodorous vaginal discharge, BV has been associated with pelvic inflammatory disease [1], infections following gynaecological surgery [2], and pre-term birth [3]. It has also been suggested that the presence of BV increases the risk for human immunodeficiency virus infection [4,5]. Treatment with metronidazole or clindamycin, administered orally or intra-vaginally, has been followed by frequent recurrences of BV [6]. Because of its high morbidity and frequent recurrence following treatment, alternative therapeutic agents need to be sought for the treatment of BV.

Probiotics are defined as ‘live microorganisms which, when administered in adequate amounts, confer a health benefit on the host’ [7]. Lactobacilli are the commonest organisms used as probiotics. Since the vaginal microbiota of women with BV has been found to contain a reduced number of lactobacilli in comparison with healthy women, lactobacilli administered orally or intra-vaginally have been tested for their effectiveness in colonising the vagina and curing women with BV, or at least preventing its recurrence.

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CHANGES IN VAGINAL MICROBIOTA DURING BV

The normal vaginal microbiota is normally dominated by lactobacilli, especially *Lactobacillus crispatus* [8–11], *Lactobacillus jenseni* [8,11], *Lactobacillus iners* [9,11,12] and *Lactobacillus gasseri* [8,10,11]. Compared with that of normal women, the vaginal microbiota of women with BV consists more commonly, and in higher numbers, of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Prevotella*, *Peptostreptococcus*, *Mobiluncus* and *Bacteroides* spp., while lactobacilli are found less frequently and in lower numbers. Nugent et al. [18] analysed the cervicovaginal lavage samples of 21 human immunodeficiency virus-positive women by real-time PCR, and found that the median number of lactobacilli was significantly lower and the median number of *G. vaginalis* organisms was significantly higher in five women with BV, compared with 16 women without BV (8.5 × 10^6 vs. 1.1 × 10^8, p = 0.013, and 1.3 × 10^10 vs. 5.4 × 10^7, p = 0.004, respectively). Mikamo et al. [19] also found that the mean count of *Lactobacillus* spp. was significantly lower in 129 *G. vaginalis*-positive women than in 110 *G. vaginalis*-negative women (7.02 vs. 8.66 log_{10} CFU/g, p < 0.0001).

It has been suggested that H_2O_2-producing vaginal lactobacilli may prevent infection of the vaginal epithelium by bacteria that cause BV. Eschenbach et al. [17] isolated facultative H_2O_2-producing vaginal lactobacilli from 27 (96%) of 28 women without BV, and from four (6%) of 67 women with BV (p < 0.001). In a study of pregnant women by Hillier et al. [20], H_2O_2-producing lactobacilli were isolated from 5% of women with BV (based on the Nugent score) and from 61% of those with a normal microbiota (p < 0.001). A second study of pregnant women by Hillier et al. [21] showed that BV (based on Amsel’s criteria) was significantly less common among women with H_2O_2-producing vaginal lactobacilli (10/127, 8%) than among women with non-H_2O_2-producing or no lactobacilli (29/86, 34%, and 37/62, 60%, respectively; p < 0.001 for both comparisons). Similarly, Hawes et al. [22] found that BV developed in ten (25%) of 40 women with non-H_2O_2-producing vaginal lactobacilli, compared with only three (3%) of 118 women with H_2O_2-producing lactobacilli (p = 0.02). Furthermore, a study by Antonio et al. [8] found that women with vaginal *L. crispatus* or *L. jenseni* (>94% of which were found to produce H_2O_2) were significantly less likely to have BV than were women colonised by other lactobacilli (only 22% of which produced H_2O_2) or women with no vaginal lactobacilli.

In contrast, some studies do not support the protective role of H_2O_2-producing lactobacilli against BV. In the study by Alvarez-Olmos et al. [14] among women with vaginal lactobacilli, H_2O_2-producing lactobacilli were isolated from 85% of 18 women with BV, and from 15% of 43 women without BV [14]. Moreover, Rosenstein et al. [23] isolated H_2O_2-producing lactobacilli from 11 (91.7%) of 12 pregnant women whose microbiota was indicative of BV following Gram’s stain.

IN-VITRO EVIDENCE FOR THE EFFECT OF VAGINAL LACTOBACILLI ON BACTERIA CAUSING BV

Some in-vitro studies have shown that specific strains of lactobacilli are able to coaggregate with
G. vaginalis and block the adherence and/or displace previously adherent strains of G. vaginalis from vaginal epithelial cells. Boris et al. [24] showed that Lactobacillus acidophilus, L. gasseri and L. jensenii, isolated from the vaginal samples of healthy pre-menopausal women, coaggregated in vitro with G. vaginalis. L. acidophilus was also found to decrease the adherence and to displace previously adherent strains of G. vaginalis on vaginal epithelial cells. Mastromarino et al. [25] found that human isolates of Lactobacillus salivarius FV2 and L. gasseri 335 coaggregated in vitro with G. vaginalis, and that vaginal tablets containing a combination of these organisms with Lactobacillus brevis CD2 (which is strongly adherent to epithelial cells) reduced the adhesion by 57.7% and displaced 60.8% of G. vaginalis cells attached previously.

Some Lactobacillus strains have also been found to have an inhibitory effect on the in-vitro growth of pathogens that cause BV, which may be caused, in part, by the production of H2O2. Mastromarino et al. [25] found that L. salivarius FV2 and L. gasseri 335, isolated from the human vagina, produced large amounts of H2O2 and inhibited the growth of G. vaginalis. McLean and Rosenstein [26] showed that L. acidophilus 48101, isolated from the vagina of healthy women, produced large amounts of H2O2 and inhibited (although by less than the mean + SD) the growth of Bacteroides spp., Prevotella bivia and G. vaginalis isolated from vaginal swabs of women with BV.

Production of lactic acid by lactobacilli, which is mainly responsible for the low vaginal pH, contributes, probably even more than production of H2O2, to the inhibition of growth of G. vaginalis. An in-vitro study by McLean and McGroarty [27] showed that the bacteriostatic effect of L. acidophilus on G. vaginalis NCTC 11292 was reduced by 60% after increasing the culture pH by the addition of NaOH, and by 30% after denaturing H2O2 with catalase. Thus, production of lactic acid, which was mainly responsible for the low pH and, to a lesser degree, production of H2O2 by L. acidophilus, affected the growth inhibition of G. vaginalis significantly. Klebanoff et al. [28] found that H2O2-producing lactobacilli at high concentrations inhibited the growth of G. vaginalis and Bacteroides bivius. Catalase inhibited the toxicity of H2O2-producing lactobacilli, but not that of non-H2O2-producing lactobacilli. Lower concentrations of H2O2-producing lactobacilli were toxic for G. vaginalis, but only when combined with myeloperoxidase and chloride, which have both been found in cervical mucus. The highest toxicity of this combination was obtained at pH 5–6. A pH of ≤4.5 had, by itself, an inhibitory effect on the growth of G. vaginalis, which was increased when the above combination was added.

Finally, production of bacteriocins by some Lactobacillus strains has also been found to play a role in the inhibition of growth of G. vaginalis, at least in vitro. Aroucheva et al. [29] tested 22 Lactobacillus strains and found that 80% produced a bacteriocin that inhibited the growth of G. vaginalis. Simoes et al. [30] showed that the growth of 28 (78%) of 36 clinical isolates of G. vaginalis was inhibited by a bacteriocin-producing L. acidophilus strain, and characterised these G. vaginalis isolates as bacteriocin-susceptible.

**CLINICAL TRIALS**

Several clinical trials have been performed to investigate whether specific strains of lactobacilli, administered either orally or intra-vaginally, are able to colonise the vaginas of women with symptomatic or asymptomatic BV, to reduce the colonisation of pathogens, and to improve symptoms and/or signs of BV when they are present. Table 1 summarises the main characteristics and outcomes of randomised controlled trials (RCTs) that have been conducted with the aforementioned purpose.

Some RCTs have suggested that intra-vaginal administration of L. acidophilus for 6–7 days cures women with BV significantly more frequently than administration of a placebo, administration of acetic acid, or no treatment. Cure of BV was defined by the absence or presence of only one of Amsel’s criteria, which are vaginal fluid with a pH >4.5, a thin homogeneous greyish-white adherent discharge, a fishy odour on addition of potassium hydroxide 10% w/v to the discharge (a positive amine test or sniff/wiff test), and clue cells on a saline wet mount [31]. Hallen et al. [32] found that significantly more women with BV were cured 7–10 days after the start of treatment with L. acidophilus when compared with those treated with a placebo. Restoration of a normal vaginal microbiota was established in significantly more (57%, 16/28) women with BV who were treated with L. acidophilus than in those receiving a placebo (none of 29). Another RCT involving pregnant
<table>
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<tr>
<th>Study</th>
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<th>Study population</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>Fredricsson et al. [39]</td>
<td>61</td>
<td>Women with BV (3/4 Amel's criteria positive)</td>
<td>Group 1 (n = 14): 5 mL of fermented milk product with <em>Lactobacillus acidophilus</em> (≥10⁷ CFU/mL) intra-vaginally twice-daily for 1 week</td>
<td>Cure (0–1 Amsel's criteria) 4 weeks after start of treatment: Group 1: 1/14 (7.1%); group 2: 3/17 (17.6%); group 3: 1/16 (6.3%); group 4: 13/14 (92.9%)</td>
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<td>Group 2 (n = 17): acetic acid jelly intra-vaginally 5 mL of 0.9% NaCl twice-daily for 1 week Group 3 (n = 16): oestrogen intra-vaginally 5 mL cream twice-daily for 1 week Group 4 (n = 14): metronidazole 500 mg, intra-vaginally twice-daily for 1 week</td>
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<td>Hallen et al. [32]</td>
<td>57</td>
<td>Women with BV (3/3 Amel's criteria positive)</td>
<td>Capsules of <em>(H₂O₅-producing)</em> <em>L. acidophilus</em> (≥10⁷ CFU/capsule) intra-vaginally twice-daily for 6 days (n = 28)</td>
<td>Presence of BV 7–10 days after start of treatment: 12/26 (46%) lactobacilli-treated vs. 2/29 (100%) placebo-treated, p &lt; 0.005</td>
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<tr>
<td>Nent et al. [33]</td>
<td>84</td>
<td>Women aged 25-31 years with BV (3/3 Amel's criteria positive)</td>
<td>Group 1 (n = 33): intra-vaginally 10–15 mL of yoghurt with <em>L. acidophilus</em> (≥10⁷ CFU/mL) and oestriol (0.03 mg/tablet) (Gynoflor) for 7 days and repetition after 1 week Group 2 (n = 32): tampons with 10–15 mL of 5% acetic acid and repetition after 1 week</td>
<td>Subjective clinical improvement on second day after start of treatment: group 1: 32/33 (100%), group 2: 20/32 (62.5%), group 3: 0/20 (0%), group 4: 0/20 (0%). p &lt; 0.0005; group 2 vs. group 3: p &gt; 0.05; group 1 vs. group 2: p &lt; 0.05; group 2 vs. group 3: p &gt; 0.05; group 1 vs. group 3: p &lt; 0.005; group 1 vs. group 4: p &lt; 0.0005; group 2 vs. group 4: p &gt; 0.05; group 3 vs. group 4: p &gt; 0.05. Cure of BV 2 months after end of second treatment: group 1: 28/32 (87.5%), group 2: 12/32 (37.5%), group 3: 1/20 (5%), p &lt; 0.05; group 1 vs. group 2: p &lt; 0.05; group 1 vs. group 3: p &lt; 0.005; group 2 vs. group 3: p &lt; 0.05; group 2 vs. group 4: p &gt; 0.05; group 3 vs. group 4: p &gt; 0.05</td>
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<td>Parent et al. [34]</td>
<td>32</td>
<td>Pre-menopausal women with BV (≥2 Amel's criteria positive, 6–30 vaginal lactobacilli per field of view [1000x magnification], eight pregnant)</td>
<td>1–2 vaginal tablets/day (n = 17)</td>
<td>Cure of BV (positive ≤1/4 Amel's criteria): 2 weeks after start of treatment: 10/13 (76.9%) lactobacilli-treated vs. 0/12 (0%) placebo, p &lt; 0.05; 4 weeks after start of treatment: 7/8 (87.5%) lactobacilli-treated vs. 0/9 (0%) placebo, p &lt; 0.05, 30% vaginal lactobacilli per field of view (1000x magnification): 2 weeks after start of treatment: 7/11 (63.6%) lactobacilli-treated vs. 1/10 (10%) placebo, p &lt; 0.05; 4 weeks after start of treatment: 7/8 (87.5%) lactobacilli-treated vs. 0/7 (0%) placebo, p &lt; 0.01. Women with positive <em>L. acidophilus</em> cultured² before treatment: 20% (group 1) vs. 31% (group 2); after 1 month: 71% (group 1) vs. 27% (group 2), p &lt; 0.05; after 2 months: 92% (group 1) vs. 27% (group 2), p &lt; 0.05. Women with BV (3/4 Amel's criteria-positive: pH &gt; 4.5, positive amine test, clue cells²) before treatment: 56% (group 1) vs. 68% (group 2); after 1 month: 24% of 21 women (group 1) vs. 52% of 19 women (group 2), p &lt; 0.05; after 2 months: 6% of 14 women (group 1) vs. 43% of 14 women (group 2), p &lt; 0.05</td>
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<td>Shalev et al. [41]</td>
<td>46</td>
<td>Women with recurrent vaginitis (≥4 episodes during the year prior to the study, 20 women with BV and eight women with VVC and BV at the start of the study)</td>
<td>Group 1 (n = 23): 150 mL/day yoghurt with <em>L. acidophilus</em> for 2 months + no yoghurt for the next 2 months</td>
<td>Before treatment: 20% (group 1) vs. 31% (group 2); after 1 month: 71% (group 1) vs. 27% (group 2), p &lt; 0.05; after 2 months: 92% (group 1) vs. 27% (group 2), p &lt; 0.05. Women with BV (3/4 Amel’s criteria-positive: pH &gt; 4.5, positive amine test, clue cells²) before treatment: 56% (group 1) vs. 68% (group 2); after 1 month: 24% of 21 women (group 1) vs. 52% of 19 women (group 2), p &lt; 0.05; after 2 months: 6% of 14 women (group 1) vs. 43% of 14 women (group 2), p &lt; 0.05</td>
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<td>Group 2 (n = 23): 150 mL/day pasteurised yoghurt for 2 months + no yoghurt for the next 2 months</td>
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<td>Group 3 (n = 23): 150 mL/day pasteurised yoghurt for 2 months + no yoghurt for the next 2 months</td>
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Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of women Study population</th>
<th>Treatment</th>
<th>Control</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Reid et al. [44]</td>
<td>42 women with no symptoms of urogenital infection during the year before the study (16 women had asymptomatic BV, based on Nugent score)</td>
<td>Group 1 (n = 10): L. rhamnosus GR-1/L. fermentum RC-14 (8 x 10^7/day orally for 28 days Group 2 (n = 12): L. rhamnosus GR-1/L. fermentum RC-14 1.6 x 10^7/day orally for 28 days Group 3 (n = 11): L. rhamnosus GR-1/L. fermentum RC-14 6 x 10^7/day orally for 28 days</td>
<td>Conversion from BV to normal Nugent score ≥ 6 (placebo)</td>
<td>RMS symptoms of BV for 6 weeks</td>
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<tr>
<td>Reid et al. [42]</td>
<td>64 women with no symptoms of urogenital infection during the year before the study (16 women had asymptomatic BV, based on Nugent score)</td>
<td>L. rhamnosus GR-1 + L. fermentum RC-14 (&gt;10^9/strain/capsule viable) orally once-daily for 60 days (n = 32)</td>
<td>Restoration from BV to normal Nugent score ≥ 6 (placebo)</td>
<td>RMS symptoms of BV for 6 weeks</td>
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<tr>
<td>Reid et al. [43]</td>
<td>59 pre-menopausal women without urogenital infections during the year prior to the study (15 women had BV, based on Nugent score)</td>
<td>L. rhamnosus GR-1 + L. fermentum RC-14 (&gt;10^9/capsule viable) orally once-daily for 60 days (n = 29)</td>
<td>Change from BV (Nugent score ≥ 7-10) to normal or intermediate vaginal microbiota (Nugent score 0-6) 2 months after start of the study: 7/8 (87.5%) lactobacilli-treated vs. 0/7 (0%) placebo-treated, p &lt; 0.05</td>
<td>No symptoms of BV for 6 weeks</td>
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<tr>
<td>Otkinay et al. [35]</td>
<td>360 women aged 17-65 years with urogenital infections (19 women with BV)</td>
<td>One vaginal tablet/day of live L. acidophilus (≥10^9 CFU/tablet) and oestrogen (0.03 mg/tablet) and lactose (600 mg/tablet) (Gynoflor) for 6 days (for post-menopausal women) (n = 240)</td>
<td>No significant improvement of vaginal symptoms (discharge, burning, itching, vulvar/ vaginal inflammation, dyspareunia) (both lactobacilli- and placebo-treated)</td>
<td>RMS symptoms of BV for 6 weeks</td>
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<tr>
<td>Eriksson et al. [40]</td>
<td>187 women aged 18-53 years with BV (≥ Amsel’s criteria positive, 68.4%; 128/187: Nugent score ≥6)</td>
<td>Tampons with L. gasseri, L. casei var. rhamnosus and L. fermentum for 25 days (n = 91)</td>
<td>Cure rate after second menstruation:</td>
<td>RMS symptoms of BV for 6 weeks</td>
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aAmsel’s criteria are: vaginal fluid with pH >4.5; thin, homogeneous, greyish-white adherent discharge; fishy odour on addition of potassium hydroxide 10% w/v to the discharge (positive amine test or sniff test); and clue cells on saline wet mount.
bThe percentages are estimated approximately based on Figs 1 and 3 of Shalev et al. [41].
cPoints 1 to 4+ are allocated to each of the following morphotypes: lactobacilli (large Gram-positive rods), Gardnerella vaginalis (small Gram-variable rods), Bacteroides spp. (small Gram-negative rods) and Mobiluncus spp. (curved Gram-variable rods). Nugent score after adding the points: 0-3, normal lactobacilli-dominant vaginal microbiota; 4-6, intermediate vaginal microbiota; and 7-10, BV.
dLactobacilli or placebo were administered 2-3 days after the end of anti-infective therapy (oral metronidazole for trichomoniasis and BV; oral fluconazole ± local ketoconazole for candidiasis).

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women with BV showed that significantly more women treated with *L. acidophilus* intra-vaginally were cured of BV at both 1 and 2 months after the end of treatment when compared with women treated with acetic acid or given no treatment [33]. Parent *et al.* [34] 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 *L. acidophilus* and oestriol, when compared with women with BV who received a placebo.

Ozkinay *et al.* [35] suggested that a healthier vaginal microbiota, consisting of higher numbers of lactobacilli and lower numbers of pathogenic bacteria, was established in women who had received *L. acidophilus* intra-vaginally and oestriol for 6–12 days, compared with those receiving a placebo, 2 or 3 days after the end of treatment of BV or trichomoniasis with oral metronidazole, and of vaginal candidiasis with oral fluconazole with or without local ketoconazole. However, no significant improvement of vaginal symptoms was observed for either group of patients.

A prospective cohort study by Chimura *et al.* [36] also yielded positive results regarding the effect of intra-vaginal administration of yoghurt containing *Lactobacillus* for 11 women with BV. A statistically significant reduction in vaginal inflammation, discharge and vaginal pH was found, and all 14 Gram-negative strains isolated initially had disappeared 3 days after treatment. Bacteriologically, BV was eradicated in six (54.5%) of the 11 women, and was partly eradicated in three (27.3%). Two other prospective cohort studies [37,38] administered *L. acidophilus* intra-vaginally in combination with vitamin B complex or oestriol to women with vaginitis, but it was not mentioned whether the women included in this latter study had BV.

In contrast, several other RCTs have failed to detect a significant difference in the cure rates for women with BV, and have detected no significant change in the number of vaginal lactobacilli, after intra-vaginal treatment with specific strains of lactobacilli, and vaginal metronidazole was found to be significantly more effective than lactobacilli in curing BV in one study. Fredricsson *et al.* [39] found that instillation of *L. acidophilus* into the vaginas of 14 women with BV cured only one (7.1%) subject, while vaginal metronidazole tablets cured 92.9%, and vaginal acetic acid jelly cured 17.6% of the women with BV who were treated with each regimen. Moreover, treatment with *L. acidophilus* did not increase the number of vaginal lactobacilli isolates. Subsequently, Eriksson *et al.* [40] used vaginal clindamycin to treat 187 women with BV, and then administered *L. gasseri, Lactobacillus casei* var *rhamnosus* and *Lactobacillus fermentum*, or a placebo, intra-vaginally during the following menstruation cycle. The BV cure rate after the second menstruation, as defined by either Amsel’s criteria or Nugent’s score, did not differ significantly for the women treated with the tested lactobacilli when compared with those treated with a placebo.

Oral administration of *L. acidophilus, Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 for 2 months has been found in other RCTs to be more effective than a placebo in preventing recurrences of BV and/or increasing vaginal colonisation with lactobacilli, thus restoring the normal vaginal microbiota. Of 46 women with recurrent vaginitis participating in a study by Shalev *et al.* [41], 28 had BV, but only seven completed the study. The percentage of women with positive *L. acidophilus* vaginal cultures after 1 month and after 2 months increased among women receiving yoghurt containing *L. acidophilus* during the first 2 months of the study, and was significantly higher than for women receiving pasteurised yoghurt during the same period. Moreover, episodes of BV after 1 and after 2 months decreased significantly in women who consumed yoghurt containing *L. acidophilus* during the first 2 months of the study when compared with the episodes of BV among women consuming pasteurised yoghurt during the same period [41].

Reid *et al.* [42] found that the numbers of vaginal lactobacilli showed a significant increase in 32 healthy women receiving *L. rhamnosus* GR-1 and *L. fermentum* RC-14 orally on a daily basis for 2 and 4 weeks compared with 32 healthy women taking a placebo. The vaginal microbiota was restored from asymptomatic BV to a normal Nugent score in significantly more women receiving lactobacilli than in placebo-treated women. A similar result was obtained in a second RCT involving 59 women treated with either the same lactobacilli at the same dosage and for the same period or with a placebo [43]. The dose of lactobacilli required to restore and maintain a normal (based on Nugent score) vaginal microbiota was found to be $>10^8$ viable *L. rhamnosus* GR-1 and *L. fermentum* RC-14 daily in a trial involving 42 healthy women [44].
Finally, *L. acidophilus* was administered intramuscularly in a small prospective cohort study by Pattman *et al.* [45]. Three 0.5-mL injections at 2-weekly intervals were administered to eight women with recurrent BV (more than two episodes during the 6-month period preceding the study) who had been treated with oral metronidazole. Six women were treated concurrently with metronidazole. Four (50%) of these women had no episodes of BV for 6 months, two had a recurrence of BV within 3 months of completing treatment, but had no more episodes after being treated with metronidazole, and one had two recurrences, received one additional injection with *L. acidophilus*, and remained asymptomatic for the following 6 months. Clue cells were replaced by lactobacilli in all women who reported improvement of their symptoms.

**CONCLUSIONS**

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. Most relevant clinical trials have suggested that oral administration of *L. acidophilus*, or intra-vaginal administration of *L. acidophilus* or *L. rhamnosus* GR-1 and *L. fermentum* RC-14, is able to increase the numbers of vaginal lactobacilli, restore the vaginal microbiota to normal, and cure women of BV, although several trials found that intra-vaginal instillation of lactobacilli had no significant effect on the treatment of BV. In most of the relevant RCTs, lactobacilli were compared with a placebo, in two RCTs with acetic acid, and in one RCT with no treatment. Interestingly, in only one RCT [39] were lactobacilli compared with metronidazole. However, further RCTs, including larger samples of women with BV, in which lactobacilli are compared either with a placebo or metronidazole, need to be conducted before it will be possible to reach definitive conclusions as to whether probiotics represent an effective and safe method for treating women with BV.

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