Probiotics for prevention of recurrent vulvovaginal candidiasis: a review

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Vulvovaginal candidiasis (VVC) is a common infection affecting the quality of life of many women. Probiotics have been investigated as possible agents for the prevention of recurrences of VVC. We reviewed the available literature. In some studies the development of VVC was associated with either a low number of lactobacilli in the vagina or with the presence of H2O2-non-producing vaginal lactobacilli, although there are a few studies not supporting these statements. In addition, in vitro studies have shown that lactobacilli can inhibit the growth of Candida albicans and/or its adherence on the vaginal epithelium. The results of some clinical trials support the effectiveness of lactobacilli, especially Lactobacillus acidophilus, Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum RC-14, administered either orally or intravaginally in colonizing the vagina and/or preventing the colonization and infection of the vagina by C. albicans, while the results of a small number of clinical trials do not corroborate these findings. Nevertheless, most of the relevant clinical trials had methodological problems such as small sample size, no control group (placebo) and inclusion of women without confirmed recurrent VVC, and thus they are not reliable for drawing definitive conclusions. Thus, the available evidence for the use of probiotics for prevention of recurrent VVC is limited. However, the empirical use of probiotics may be considered in women with frequent recurrence of VVC (more than three episodes per year), especially for those who have adverse effects from or contraindications for the use of antifungal agents, since adverse effects of probiotics are very rare. In any case women should be clearly informed about the unproven usefulness of probiotics for this purpose. In conclusion, despite the promising results of some studies, further research is needed to prove the effectiveness of probiotics in preventing the recurrences of VVC and to allow their wide use for this indication.

Keywords: candidal vaginitis, yeast vaginitis, fungal infections, lactobacilli, bifidobacteria

Introduction

Vulvovaginal candidiasis (VVC) is a common infection among women that is associated with considerable morbidity and healthcare cost. A survey by Foxman et al.1 in the US showed that 6.5% and 8% of women older than 18 years reported ≥1 and ≥4 episodes of VVC during the 2 months and 1 year prior to the survey, respectively. In addition, the total annual cost (in 1995) for dealing with VVC was estimated at $1.8 billion. The high incidence and associated healthcare cost of VVC highlight the need for the development of effective agents for its prevention.

Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host.2 There is strong evidence that Lactobacillus rhamnosus GG is effective for the treatment of acute rotavirus diarrhoea in children, causing a significant reduction of its duration.2 In addition, their usefulness for the prevention and/or treatment of many other diseases, such as antibiotic-associated diarrhoea (Saccharomyces boulardii), Helicobacter pylori infections, inflammatory bowel diseases, allergy, cancer, urinary tract infections and bacterial vaginosis, is under research.2

In the present review we tried to compile and summarize the existing data regarding the potential use of probiotics for the prevention of VVC. Many women who suffer from VVC already use these agents without prescription. In a survey carried out by Pirotta et al., 73% of 1117 women in the age range 18–70 years self-reported having had symptoms of VVC in the past and 35% reported that these symptoms appeared after an antibiotic course. Lactobacillus products were used by 40% and 43% of these women for prevention and treatment of post-antibiotic vulvovaginitis, respectively.3

It should be mentioned that the names of some lactobacilli strains have changed recently. Lactobacillus acidophilus RC-14 and Lactobacillus fermentum RC-14 studied in the Netherlands
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The results of some studies associated VVC either with a reduced number of lactobacilli or with species of lactobacilli not producing H$_2$O$_2$. In a study of 7918 pregnant women, Hillier et al. found that VVC was associated either with normal vaginal microbiota (dominated by lactobacilli) or with intermediate flora (with decreased lactobacilli). Some other studies suggested that pregnant or post-term women whose vaginas were colonized by H$_2$O$_2$-producing lactobacilli were less likely to have symptomatic VVC than those colonized with H$_2$O$_2$-non-producing vaginal lactobacilli. However, Hawes et al. suggested that H$_2$O$_2$-producing lactobacilli do not protect against VVC. In a study of 182 women visiting a sexually transmitted disease clinic, 25 of whom developed VVC during a 2 year follow-up, the absence of lactobacilli from the vagina was not found to increase the incidence of VVC.

In vitro experiments

There are some in vitro experiments which show that some lactobacilli strains can inhibit the adherence and/or the growth of C. albicans. However, these results do not necessarily apply to humans, since the physiological and pathophysiological mechanisms taking place in humans are more complex and cannot be accurately imitated in the laboratory.

Osset et al. found that 8 of 15 studied lactobacilli inhibited significantly the adhesion of C. albicans Y18 to vaginal cells. They also found that some lactobacilli inhibited the growth of C. albicans Y18 in liquid assays, but not in solid assays. Strus et al. found that Lactobacillus delbrueckii, which produces large amounts of H$_2$O$_2$, inhibited the growth of C. albicans more strongly and quickly than many other studied strains isolated from the vaginas of healthy women, while Lactobacillus plantarum, which does not produce H$_2$O$_2$, showed the most prolonged inhibitory activity starting after 24 h. Boris et al. found that L. acidophilus, Lactobacillus gasseri and L. jensenii, isolated from the vaginas of healthy premenopausal women, coaggregated in vitro with C. albicans, isolated from the same vaginal samples. The adherence of C. albicans on the vaginal epithelial cells, collected from the same women, was greatly decreased when L. acidophilus was added in comparison with the adherence observed when only Candida was present. Adherence on the vagina is an important virulence factor of C. albicans; thus, reducing its adherence may prevent VVC. Coaggregation of lactobacilli with Candida may also be important for the prophylaxis against vaginal infections by preventing the binding of Candida to the receptors of the vaginal epithelium.

Some substances produced by specific lactobacilli strains have been found to exert an inhibitory effect upon C. albicans, at least in vitro. Velaarss et al. found that the initial adherence rates of two C. albicans strains, suspended in a urine sample, on a silicone rubber filled with a biosurfactant of L. acidophilus RC-14 (‘surlactin’), 4 h after low urine flow, decreased by 50% compared with the adherence rates on a silicone rubber without surlactin, although the numbers of adhering Candida cells were similar between the two rubbers. Oukkers et al. found that ‘pentocin TV35b’, a bacteriocin-like peptide isolated from Lactobacillus pentosus, inhibited the growth of C. albicans. Reid et al. suggested that a biosurfactant produced by L. fermentum RC-14 inhibits the adhesion of C. albicans.
Clinical studies

In Table 1 we present some clinical trials that have been conducted in order to evaluate the ability of orally or intravaginally administered lactobacilli to inhibit the vaginal colonization by yeast and prevent the recurrence of VVC. Reid et al.\textsuperscript{23} reported the case of a 33-year-old woman with recurrent cystitis and VVC (20 episodes of VVC in 30 months), whose vagina was colonized by \textit{L. casei} var. \textit{rhamnosus} GR-1 up to 7 weeks after the vaginal administration of one pessary of these lactobacilli. The woman had no symptoms of vaginitis during this period and for the next 6 months during which two more pessaries were inserted into her vagina.

A clinical trial suggesting the effectiveness of vaginal lactobacilli for the treatment of VVC was conducted by Hilton et al.,\textsuperscript{24} who administered vaginal suppositories of \textit{Lactobacillus} GG twice per day for 7 days to 28 women with symptoms and signs of VVC at the start of the study and a history of recurrent VVC (>5 per year). A serious limitation of this study was that only 5 of these women had considerable colonies of \textit{C. albicans} at the start of the study, maybe because 15 of the studied women had taken antifungal agents just before the study. All of them reported improvement of their vaginal symptoms and were found to have reduced vaginal erythema and discharge during clinical examination. Four of the five women with positive vaginal cultures had negative cultures after receiving lactobacilli. However, no conclusions can be drawn from this study due to its poor design and the small sample of studied women with confirmed VVC.

Williams et al.\textsuperscript{25} also examined the ability of intravaginally administered lactobacilli to reduce the VVC risk in a double-blind, placebo-controlled trial of 164 HIV-positive women, a group of patients in whom recurrent VVC is common. The women were randomized into three groups: the first group received intravaginally \textit{L. acidophilus} GG twice per week for 14 days in 10 women with recurrent VVC and bacterial vaginosis. The women were randomized into two groups; the first group received daily 8 ounces of yogurt with \textit{L. acidophilus} for 6 months and did not consume any yogurt for the 6 following months, and the other group consumed first the yogurt-free and then the yogurt-containing diet. The mean number of candidal infections and the mean number of candidal colonizations of the vagina and rectum per woman were significantly less during the 6 months of yogurt consumption in comparison with the 6 months without receiving yogurt (0.38 versus 2.54, \(P = 0.001\) and 0.84 versus 3.23, \(P = 0.001\), respectively). However, the fact that the vaginal colonization by \textit{Lactobacillus} was not statistically significantly increased during yogurt intake and that the studied women were not blinded makes it difficult to interpret the results of this study.

On the other hand, there are a few studies that do not support a role for probiotics in the prevention of recurrent VVC. Shalev \textit{et al.}\textsuperscript{20} studied 46 women with recurrent vaginitis (24 episodes during the year prior to the study), 18 of whom had VVC and 8 had VVC and bacterial vaginosis. The women were randomized into 2 groups of 23 women; the first group received 150 mL/day yogurt with \(>10^8\) cfu/mL live \textit{L. acidophilus} for 2 months and the second group received 150 mL/day of a pasteurized yogurt for the same period. For the next 2 months women of both groups did not consume any yogurt. For the last 2 months of the study the first group consumed pasteurized yogurt and the second group yogurts with lactobacilli. During the first 4 months 28 women took part in the study and only 7 completed the whole protocol. The percentage of women with positive \textit{L. acidophilus} vaginal cultures among the first group increased after the first 1 and 2 months of the study and was significantly higher than that of the second group. Although a progressive decrease in positive vaginal cultures for \textit{Candida} was found in both groups, the percentage of women with positive \textit{Candida} cultures after the first 1 and 2 months of the study was not significantly different between the two groups. However, in this trial no consideration was given to the properties of the tested lactobacilli strain against 4 women were dominated by lactobacilli. One week after the beginning of the trial, lactobacilli dominated the vagina of all women and GR-1 and/or RC-14 were recovered from all of them. No recurrences of yeast vaginitis appeared during the study and follow-up.

Reid \textit{et al.}\textsuperscript{28} supported the possible ability of orally administered \textit{L. rhamnosus} GR-1 and \textit{L. fermentum} RC-14 (at a dose of more than \(8 \times 10^8\) viable lactobacilli) to restore and maintain a normal vaginal microbiota in a randomized clinical trial in 42 women in the age range 17–50 years without symptoms of urogenital infection at the start and during the study, 33 of whom reported a history of VVC. The women were randomly separated into four groups; groups 1, 2 and 3 received daily orally capsules of GR-1/RC-14 at different dosages and group 4 received daily one capsule of \textit{L. rhamnosus} GG. Of the women who had a normal vaginal microbiota at the beginning of the study, 92% (12/13) of the GR-1/RC-14-treated and 50% (2/4) of the GG-treated remained normal within 28 days. Of the women who had a history of yeast vaginitis in the 5 years prior to the study and an abnormal vaginal microbiota at the start of the study, 54% (7/13) of the GR-1/RC-14-treated and 25% (1/4) of the GG-treated developed a normal vaginal microbiota within 28 days.

Hilton \textit{et al.}\textsuperscript{29} found that \textit{L. acidophilus} can reduce the vaginal colonization and infection by \textit{Candida} in a clinical trial in 33 women with recurrent candidal vaginitis (≥2/year), 13 of whom completed the study. The studied women were randomized into two groups; the first group received daily 8 ounces of yogurt with \textit{L. acidophilus} for 6 months and did not consume any yogurt for the 6 following months, and the other group consumed first the yogurt-free and then the yogurt-containing diet. The mean number of candidal infections and the mean number of candidal colonizations of the vagina and rectum per woman were significantly less during the 6 months of yogurt consumption in comparison with the 6 months without receiving yogurt (0.38 versus 2.54, \(P = 0.001\) and 0.84 versus 3.23, \(P = 0.001\), respectively). However, the fact that the vaginal colonization by \textit{Lactobacillus} was not statistically significantly increased during yogurt intake and that the studied women were not blinded makes it difficult to interpret the results of this study.
Table 1. Characteristics of reviewed studies

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Type of study</th>
<th>No. of women studied</th>
<th>Study population</th>
<th>Intervention</th>
<th>Symptoms and signs of VVC after intervention</th>
<th>Cultures of vaginal swabs after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilton (1993) 24</td>
<td>prospective cohort</td>
<td>24</td>
<td>recurrent VVC (&gt;5/year) and symptoms of VVC (positive cultures for <em>Candida</em> in 5 women)</td>
<td>vaginal suppositories with <em>Lactobacillus</em> GG twice/day for 7 days</td>
<td>improvement of symptoms and signs (of erythema and discharge)</td>
<td>4/5 women with cultures positive for <em>Candida albicans</em> before intervention; negative cultures 7 days after the completion of intervention</td>
</tr>
<tr>
<td>Williams (2001) 25</td>
<td>randomized controlled trial</td>
<td>164</td>
<td>HIV-positive</td>
<td>group 1 (58 women): vaginal <em>L. acidophilus</em> weekly; group 2 (50 women): vaginal clotrimazole weekly; group 3 (56 women): placebo</td>
<td>cases of VVC (culture-confirmed) in 21 months (median) of follow up; group 1: 9/58 (15.5%); group 2: 7/50 (14%); group 3: 18/56 (32.1%)</td>
<td>34 culture-confirmed cases of VVC in 21 months relative risk for development of VVC: group 1 compared with group 3: 0.5; group 2 compared with group 3: 0.4</td>
</tr>
<tr>
<td>Reid (2003) 26</td>
<td>randomized controlled trial</td>
<td>64</td>
<td>no urogenital infection in the year prior to the study</td>
<td>group 1 (32 women): <em>L. rhamnosus</em> GR-1 + <em>L. fermentum</em> RC-14 orally once/day for 60 days; group 2 (32 women): placebo</td>
<td>improvement of vaginal symptoms: 30% (group 1) versus 12% (group 2)</td>
<td>4 weeks after start of intervention: increase in vaginal lactobacilli: group 1 &gt; group 2 (<em>P</em> = 0.01), decrease in vaginal <em>Candida</em>: group 1 &gt; group 2 (<em>P</em> = 0.01)</td>
</tr>
<tr>
<td>Reid (2001) 27</td>
<td>prospective cohort</td>
<td>10</td>
<td>recurrent urogenital infections (9 with recurrent VVC)</td>
<td>group 1 (n = 10): GR-1/RC-14 orally twice/day for 14 days; group 2 (n = 12): GR-1/RC-14 8 × 10⁹/day orally for 28 days; group 3 (n = 11): GR-1/RC-14 1.6 × 10⁹/day orally for 28 days; group 4 (n = 9): <em>GG</em> 10¹⁰/day orally for 28 days</td>
<td>no symptoms of VVC</td>
<td>5/5 women with history of recurrent VVC &amp; low or no lactobacilli before intervention had normal number of lactobacilli 1 week after start of intervention normal vaginal flora 28 days after start of intervention: 12/13 of groups 1, 2 &amp; 3 versus 2/4 of group 4 with normal vagina at the start of the study, 7/13 of groups 1, 2 &amp; 3 versus 1/4 of group 4 with abnormal vagina at the start of the study and VVC within 5 years prior to the study</td>
</tr>
<tr>
<td>Reid (2001) 28</td>
<td>randomized controlled trial</td>
<td>42</td>
<td>no symptoms of urogenital infection at the start of the study (history of VVC in 33 women)</td>
<td>group 1 (n = 10): GR-1/RC-14 8 × 10⁹/day orally for 28 days; group 2 (n = 12): GR-1/RC-14 1.6 × 10⁹/day orally for 28 days; group 3 (n = 11): GR-1/RC-14 6 × 10⁹/day orally for 28 days; group 4 (n = 9): <em>GG</em> 10¹⁰/day orally for 28 days</td>
<td>no symptoms of VVC</td>
<td>5/5 women with history of recurrent VVC &amp; low or no lactobacilli before intervention had normal number of lactobacilli 1 week after start of intervention normal vaginal flora 28 days after start of intervention: 12/13 of groups 1, 2 &amp; 3 versus 2/4 of group 4 with normal vagina at the start of the study, 7/13 of groups 1, 2 &amp; 3 versus 1/4 of group 4 with abnormal vagina at the start of the study and VVC within 5 years prior to the study</td>
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Hilton (1992) randomized controlled trial

33 recurrent VVC (≥5/year)

- Group 1: 8 ounces/day yogurt of *L. acidophilus* for 6 months then no yogurt for the next 6 months
- Group 2: no yogurt for 6 months then 8 ounces/day yogurt of *L. acidophilus* for the next 6 months

Mean number of VVC during 6 months receiving yogurt smaller than that during 6 months not taking yogurt (0.38 versus 2.54, *P* = 0.001)

Mean number of candidal colonization of vagina & rectum/woman during 6 months receiving yogurt < during 6 months not taking yogurt (0.84 versus 3.23, *P* = 0.001)

Shalev (1996) randomized controlled trial

46 recurrent (≥4 in the last year) vaginitis (VVC: *n* = 18, VVC & bacterial vaginosis: *n* = 8)

- Group 1 (n = 23): 150 mL/day yogurt with *L. acidophilus* for 2 months then no yogurt for the next 2 months then pasteurized yogurt for the last 2 months
- Group 2 (n = 23): pasteurized yogurt for 2 months then no yogurt for the next 2 months then 150 mL/day yogurt with *L. acidophilus* for the last 2 months

Positive cultures for *L. acidophilus*:
- Before intervention: 20% (group 1) versus 31% (group 2)
- After 1 month: 71% (group 1) versus 27% (group 2), *P* < 0.05
- After 2 months: 92% (group 1) versus 30% (group 2), *P* < 0.05

Positive cultures for Candida:
- Before intervention: 56% (group 1) versus 62% (group 2)
- After 1 month: 44% (group 1) versus 37% (group 2), *P* > 0.05
- After 2 months: 21% (group 1) versus 28% (group 2), *P* > 0.05

Pirotta (2004) randomized placebo-controlled double-blind trial

278 treatment with antibiotics for non-gynaecological infections

- Group 1 (n = 67): *L. rhamnosus* & *Bifidobacterium longum* orally twice/day + *L. rhamnosus*, *L. delbrueckii*, *L. acidophilus* & *Streptococcus thermophilus* vaginally once/night for 10 days
- Group 2 (n = 70): *L. rhamnosus*, *L. delbrueckii*, *L. acidophilus* & *Streptococcus thermophilus* vaginally once/night + placebo orally twice/day for 10 days
- Group 3 (n = 73): *L. rhamnosus* & *Bifidobacterium longum* orally twice/day + placebo vaginally once/night for 10 days
- Group 4 (n = 68): placebo twice/day orally + once/night vaginally for 10 days

Vaginal symptoms after 14 days:
- Group 1: 15/67 (22%)
- Group 2: 18/70 (27%)
- Group 3: 17/73 (25%)
- Group 4: 22/68 (34%)

Positive Candida cultures after 14 days:
- Group 1: 16/67 (24%)
- Group 2: 17/70 (24%)
- Group 3: 17/73 (23%)
- Group 4: 9/68 (13%)
Candida; thus, it is difficult to draw conclusions regarding the effectiveness of probiotics against VVC.

Pirotta et al.31 also did not support the use of combinations of specific lactobacilli, either given orally or intravaginally, for the prevention of post-antibiotic vulvovaginitis. They conducted a randomized, placebo-controlled, double-blind clinical trial in non-pregnant women in the age range 18–50 years who received oral powder of L. rhamnosus and Bifidobacterium longum (Lactobac) twice daily and/or one vaginal pessary of L. rhamnosus, L. delbrueckii, L. acidophilus and Streptococcus thermophilus (Femilac) each night and/or oral and/or intravaginal placebo during 6 days of antibiotic administration for a non-gynaecological infection and for 4 days afterwards. Four days after completion of the intervention, post-antibiotic vulvovaginitis had developed in 23% (55/235) of the studied women [95% confidence interval (CI) 18–29%]. The OR for developing post-antibiotic vulvovaginitis was 1.06, while receiving oral lactobacilli (95% CI 0.58–1.94), and 1.38, while receiving vaginal lactobacilli (95% CI 0.75–2.54), in comparison with placebo.

A careful review of the studies investigating the role of probiotics in the prevention of recurrent VVC suggests that most of them have important methodological shortcomings. In the majority of the studies only a small sample of women was included or completed the study.27,29,30 Moreover in most of the studies it was not mentioned whether the reported episodes of recurrent VVC prior to the trials were confirmed by cultures of the vaginal fluids or they were just self-diagnosed by the studied women.24,27–30 Furthermore, there was no control group in some of the studies, so as to compare the women receiving lactobacilli with others receiving placebo.24,27,28

Finally, it is worth mentioning that the studies by Williams et al. and Pirotta et al. did not examine the ability of probiotics to prevent recurrences in women who already had recurrent VVC, but the efficacy of specific probiotics to prevent the development of VVC in women at high risk for such infections, specifically HIV-positive and women receiving antibiotics.25,31 In addition, the study by Reid et al.26 in 2003 addressed the potential effectiveness of two specific lactobacilli to prevent development of VVC in healthy women.

Adverse effects of probiotics

Probiotics are generally considered to be safe. However, some probiotic species have been rarely isolated from infectious sites. A study showed that only in a mean of 0.2% of positive blood cultures in Finland during 1995–2000 were Lactobacillus isolates reported.22 Apart from lactobacillaemia, infectious endocarditis, liver abscess, and fungaemia are some infections which have been associated with probiotics. These cases appear mainly in patients with serious underlying diseases and/or immunosuppression.33,36,37 Moreover, only a few cases have been reported, which associate consumed lactobacilli with those isolated from infectious sites.34,38 Generally, the cases of infections associated with probiotics are scarce in comparison with the considerable and gradually increasing consumption of probiotics.52

Conclusions

In conclusion, it is still controversial whether probiotics can prevent recurrences of VVC, while there may be more pathophysiological basis for their effectiveness in the prevention of BV.

Lactobacilli have been frequently found to co-exist with Candida in the vaginal epithelium of women with VVC, while they are significantly reduced in women with BV. Some in vitro studies and clinical trials had positive results regarding the effectiveness of some specific lactobacilli strains against C. albicans. However, most of the trials either included a small sample of women or women with no confirmed episodes of VVC or were not placebo-controlled. Moreover, there were differences among the trials regarding the strain of the tested probiotic, its dosage and the duration of treatment. It should be emphasized that the various probiotic strains have different properties and different effects on Candida; thus, results from studies testing one strain should not be extrapolated to other strains. Consequently, it is difficult to draw reliable conclusions from the existing studies. Probiotics, especially L. acidophilus, L. rhamnosus GR-1 and L. fermentum RC-14, may be considered as potential empirical preventive agents in women who suffer from frequent episodes of VVC (more than three episodes per year), since adverse effects from their use are scarce, especially when the use of antifungal agents is contraindicated or is associated with adverse effects. However, more randomized, double-blind, placebo-controlled trials with a larger sample size should be carried out, so as to clarify whether probiotics can be used effectively and safely for the prophylaxis of recurrent episodes of VVC.

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Transparency declarations

None to declare.

References

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