Probiotics for prevention of recurrent vulvovaginal candidiasis: a review

Matthew E. Falagas1,2*, Gregoria I. Betsi1 and Stavros Athanasiou3

1Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece; 2Department of Medicine, Tufts University School of Medicine, Boston, MA, USA; 31st Department of Obstetrics and Gynaecology, Athens University School of Medicine, Athens, Greece

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 included 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. in the US showed that 6.5% and 8% of women older than 18 years reported ≥1 and ≥2 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. 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. 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. 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.

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
and Canada were renamed as *Lactobacillus reuteri* RC-14 and *Lactobacillus casei* GR-1 and *L. casei* var. *rhamnosus* was renamed as *L. rhamnosus* GR-1. However, in our review we used the names of lactobacilli strains as they were mentioned in the cited articles.

### Literature search

We searched for articles in the PubMed (1975–1/2006), from which we also found some additional relevant references. The keywords were ‘vulvovaginal candidiasis’, ‘candidal vaginitis’, ‘yeast vaginitis’, ‘fungal infections’, ‘probiotics’, ‘lactobacilli’, ‘bifidobacteria’. We focused on microbiological studies and clinical trials. Specifically, we found relevant information from original articles and reviews regarding the role of endogenous lactobacilli both in normal and in *Candida*-infected vaginal flora, *in vitro* experiments investigating the effect of probiotics on the growth and adherence of *Candida albicans* on the vaginal epithelium, human studies examining the ability of orally or intravaginally administered probiotics to prevent recurrent VVCs and adverse effects of probiotics.

### Vaginal lactobacilli and pathogenesis of VVC

Lactobacilli, especially *Lactobacillus crispatus*,4–7 *Lactobacillus jensenii*12 and *Lactobacillus iners*,5,7,8 are most commonly the dominant microorganisms in the vagina of healthy premenopausal women. Lactobacilli produce lactic acid and other substances, which maintain a low pH in the vagina, thus preventing the overgrowth of pathogens, at least those causing bacterial vaginosis (BV) and gonorrhoea. *C. albicans* may also be found in the vagina of healthy premenopausal women. In a study of premenopausal women by Sobel et al., *C. albicans* was isolated from 25% of 20 healthy women.9

Although the pathogenesis of VVC remains a controversial issue, it seems that when the balance between the microorganisms existing in the vaginal microbiota is disrupted, the overgrowth of *Candida* is facilitated. Antibiotic therapy, spermicide use, oral contraceptives, oestrogen therapy, diabetes mellitus, tight clothing and frequent sexual intercourse are factors that increase the risk for development of VVC.10 Women with VVC complain about thick white caseous vaginal discharge and pruritus, and often dyspareunia, vulvar erythema and swelling. Similar symptoms and signs also occur in women with BV, thus leading to frequent misdiagnosis of BV as VVC, especially when it occurs after antibiotic therapy.

It has been suggested in some studies that lactobacilli are quite common even in the vaginal epithelium of women with VVC. Sobel et al. found that lactobacilli were the dominant vaginal microorganisms in 90% of 20 healthy premenopausal women and in 96% of 24 premenopausal women with acute exacerbations of recurrent VVC.9 However, the composition of lactobacilli species and/or strains was different between healthy women and those with VVC. The vaginal microbiota of healthy women was more frequently dominated by *Lactobacillus salivarius* (isolation rate 35%), while the vagina of women with VVC was more commonly dominated by *Lactobacillus cateniforme* (isolation rate 42%).9 Demirezen et al.11 found that presence of lactobacilli was more common among 59 studied women with VVC than among 391 healthy women.

### Review

The results of some studies associated VVC either with a reduced number of lactobacilli or with species of lactobacilli not producing H₂O₂. 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).13 Some other studies suggested that pregnant13,14 or post-term15 women whose vaginas were colonized by H₂O₂-producing lactobacilli were less likely to have symptomatic VVC than those colonized with H₂O₂-non-producing vaginal lactobacilli. However, Hawes et al.16 suggested that H₂O₂-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.17 found that 8 of 15 studied lactobacilli inhibited significantly the adherence 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.18 found that *Lactobacillus delbrueckii*, which produces large amounts of H₂O₂, 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 H₂O₂, showed the most prolonged inhibitory activity starting after 24 h. Boris et al.19 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.19

Some substances produced by specific lactobacilli strains have been found to exert an inhibitory effect upon *C. albicans*, at least *in vitro*. Velraeds 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.20 Ockers et al. found that ‘pentocin TV35b’, a bacteriocin-like peptide isolated from *Lactobacillus pentosus*, inhibited the growth of *C. albicans*.21 Reid et al.22 suggested that a biosurfactant produced by *L. fermentum* RC-14 inhibits the adhesion of *C. albicans*.267
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. 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 L. casei var. 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., who administered vaginal suppositories of 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 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 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. 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 L. acidophilus once per week, the second received vaginal clotrimazole weekly and the third took placebo (control group). During 21 months of the study, 34 cases of VVC were diagnosed clinically and microbiologically. The relative risk of developing VVC was 0.5 for the lactobacilli-treated and 0.4 for the clotrimazole-treated women as compared with the control group. Moreover, the median time until the first episode of VVC was longer for women who received lactobacilli than for those who took placebo, but the difference was not statistically significant (P = 0.09).

Some other studies have investigated the ability of orally administered lactobacilli to colonize the vagina and/or reduce the vaginal colonization and infection by Candida. Reid et al. conducted a randomized trial in 64 healthy women in the age range 19–46 years without any urogenital infections in the year prior to the study. For 60 days 32 of the studied women received orally daily L. rhamnosus GR-1 and L. fermentum RC-14, while the other 32 women received placebo. Cultures of the vaginal swabs of the studied women 4 weeks after the administration showed a significant increase in vaginal lactobacilli (P = 0.01) and a significant reduction in yeast (P = 0.01) in the lactobacilli-treated compared with the placebo-treated women.

In another clinical trial, Reid et al. administered L. rhamnosus GR-1 and L. fermentum RC-14 (×10^10 viable) orally twice daily for 14 days in 10 women with recurrent urogenital infections, 9 of whom had recurrent yeast vaginitis. The vaginal microbiota of 5 of those 9 women with recurrent VVC had <10 colonies or no lactobacilli at the start of the study, while the vaginas of the other 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 et al. supported the possible ability of orally administered L. rhamnosus GR-1 and L. fermentum RC-14 (at a dose of more than 8 × 10^5 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 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 et al. found that L. acidophilus can reduce the vaginal colonization and infection by Candida in a clinical trial in 33 women with recurrent candidal vaginitis (≥5/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 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 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 et al. studied 46 women with recurrent vaginal candidiasis (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 >10^9 cfu/mL live 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 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 Candida was found in both groups, the percentage of women with positive 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...
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)³⁴</td>
<td>prospective cohort</td>
<td>28</td>
<td>recurrent VVC (&gt;5/year) and symptoms of VVC (positive cultures for Candida in 5 women)</td>
<td>vaginal suppositories with Lactobacillus GG twice/day for 7 days</td>
<td>improvement of symptoms and signs (¹ of erythema and discharge)</td>
<td>4/5 women with cultures positive for Candida albicans before intervention: negative cultures 7 days after the completion of intervention</td>
</tr>
<tr>
<td>Williams (2001)³⁵</td>
<td>randomized controlled trial</td>
<td>164</td>
<td>HIV-positive</td>
<td>group 1 (58 women): vaginal L. acidophilus 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)³⁶</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): L. rhamnosus GR-1 + L. fermentum 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 (P = 0.01), decrease in vaginal Candida: group 1 &gt; group 2 (P = 0.01)</td>
</tr>
<tr>
<td>Reid (2001)³⁷</td>
<td>prospective cohort</td>
<td>10</td>
<td>recurrent urogenital infections (9 with recurrent VVC)</td>
<td>group 1 (9): L. rhamnosus GR-1 + L. fermentum RC-14 orally twice/day for 14 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>
</tbody>
</table>
Hilton (1992) randomized controlled trial

- Recurrent VVC (≥5/year)

  - Group 1: 8 ounces/day yogurt *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 *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

- 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

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

- 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%)
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. 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. Moreover, only a few cases have been reported, which associate consumed lactobacilli with those isolated from infectious sites. Generally, the cases of infections associated with probiotics are scarce in comparison with the considerable and gradually increasing consumption of probiotics.

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.

Acknowledgements

Funding: none.

Transparency declarations

None to declare.

References

Review