

# Prebiotics and Probiotics in Vulvovaginal Infections

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## ABSTRACT

**Aim:** To discuss the role of prebiotics and probiotics in vulvovaginal infections.

**Background:** Depletion of vaginal microflora in healthy women can lead to various vulvovaginal infections (VVI). Probiotics such as Lactobacilli are used successfully in treatment and prevention of VVIs. Prebiotics are nutrient substrates for probiotics.

**Review results:** Different strains of Lactobacilli possess different activities (pathogen displacement, bactericidal, and immunostimulatory) that are beneficial in women with VVIs. In nonpregnant women, probiotics administration either orally or vaginally improves clinical, mycological cure rate, and also reduces the recurrences in VVIs. In pregnant women also, probiotics are useful for bacterial vaginosis (BV). In pregnant women, it improves glucose metabolism and might be useful in cases with preterm premature rupture of membranes.

**Conclusion:** In VVIs, intravaginal microbial environment is dysregulated. Upregulating this microflora environment with the use of pre- and probiotics, referred as synbiotics, increases treatment success rate and helps in prevention of recurrences.

**Clinical significance:** Probiotic and prebiotic combination can be considered as one of the essential aspects in the management of VVIs.

**Keywords:** Bacterial vaginosis, Pregnancy, Probiotics, Synbiotics, Vulvovaginal infections.

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## BACKGROUND

According to the World Health Organization (WHO), probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.<sup>1</sup> Intake of probiotics can be done in routine diet or in the form of supplements.<sup>2</sup> They are effective for the management of various gastrointestinal (GI) disorders (e.g., irritable bowel syndrome and prevention of diarrhea associated with *Clostridium difficile* infection).<sup>3,4</sup> In recent years, there has been a lot of research to assess the effects of probiotics in the obstetrical and gynecological conditions. Oral or vaginal administration of probiotics helps in the prevention and treatment of vaginal infections. They also help in the prevention of preterm birth.<sup>2,5-8</sup> The ingested probiotic microorganisms survive through the GI system ascend to the vaginal tract once they are excreted from the rectum. Administered vaginally, there is a direct and targeted colonization that assists restoration of healthy vaginal flora.<sup>9</sup> With evolving evidence, the use of probiotics is expanding gradually.<sup>10</sup> Even in pregnant women, regular use of probiotics during gestation is reported.<sup>11</sup>

Vulvovaginal infections (VVI) are associated with imbalance of normal vaginal flora. Bacterial vaginosis (BV) is associated with increased vaginal pH and displacement of normal vaginal Lactobacilli flora with anaerobic bacteria.<sup>12</sup> Compared to healthy women, women with BV may have nearly 1,000 times more anaerobic bacteria.<sup>13-15</sup> In aerobic vaginitis (AV), there is absence of the normal lactobacillary flora, with predominance of aerobic microorganisms [e.g., *Escherichia coli*, *Streptococcus aureus*, group B *Streptococcus* (GBS), Enterococci].<sup>16</sup> In recent years, recurrent, severe, vulvovaginal candidiasis (VVC) has increased significantly especially those caused non-*Candida albicans* species and have become troublesome to manage.<sup>17,18</sup> In healthy women, Lactobacillus spp. are the predominant microflora in the vagina. During different VVIs, normal flora is depleted, and thus, oral or vaginal use of probiotic *Lactobacillus* strains has emerged in both treatment and prevention of such infections.<sup>19,20</sup> Prebiotics serve

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to be nonliving substrates providing nutrients for the administered probiotic strains and healthy commensal flora.<sup>21</sup> Given the role of prebiotic and probiotics in the treatment and prevention of VVIs, we reviewed current evidence for the combined use of pre- and probiotics in different VVIs.

## REVIEW RESULTS

### Rationale for Synbiotics in VVIs

A synbiotic is a blend of probiotics and prebiotics that improves the survival and activity of resident microorganisms in the gut benefiting the host.<sup>22</sup> Prebiotics are generally food-grade compounds [e.g., inulin and other fructo-oligo-saccharides

**Table 1:** Effects of Lactobacilli in VVIs

Effect observed in experimental models	Species of <i>Lactobacillus</i>						
	<i>L. acidophilus</i>	<i>L. rhamnosus</i>	<i>L. gasseri</i>	<i>L. crispatus</i>	<i>L. jensenii</i>	<i>L. reuteri</i>	<i>L. vaginalis</i>
Adhesion to epithelial cells	Y	Y	Y	Y	Y		Y
Pathogen displacement	Y		Y	Y	Y		
Bactericidal	Y	Y	Y				
Immunostimulation	Y	Y					
Anti- <i>Candida</i> effect		Y	Y	Y			

**Table 2:** International guidelines defining the role of probiotics in for the treatment of VVIs

Guideline	Year	Remarks
Centers for Disease Control and Prevention <sup>31</sup>	2015	Current evidence does not support the role of probiotics in management of bacterial vaginosis and there is need to generate more research
Society of Obstetrician and Gynecologist of Canada <sup>32</sup>	2015	Current evidence with probiotics in management of bacterial vaginosis is limited
German Society for Gynaecology and Obstetrics <sup>33</sup>	2015	Evidence with probiotics is encouraging, but controversial. There is need to generate more evidence from randomized studies
Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynecologist <sup>34</sup>	2012	Current evidence is insufficient to recommend the use of probiotics in recurrent bacterial vaginosis or vulvovaginal candidiasis
International Union against Sexually Transmitted Infection and the World Health Organization <sup>35</sup>	2011	Probiotics administered by vaginal route have a potential role for the treatment of recurrent bacterial vaginosis

(FOS), galactooligosaccharides (GOS), raffinose, lactulose, etc.]. They stimulate the native commensal bacteria in the intestines (*Bifidobacteria* and Lactobacilli)<sup>23</sup> and also promote commensal *Lactobacillus* growth in vagina.<sup>24</sup> Various *Lactobacillus* strains possess probiotic properties. Table 1 shows the effect of different Lactobacilli on different VVIs.<sup>25</sup> In an *in-vitro* study assessed action of the two probiotic strains against different pathogens responsible for BV or AV. The strain *Lactobacillus acidophilus* LMG S-29159 had highest antagonistic effect on the microbes responsible. The combination of *Lactobacillus rhamnosus* SD5675 and *L. acidophilus* LMG S-29159 was showed to inhibit the growth of all the tested pathogens (*Gardnerella vaginalis*, *Atopobium vaginae*, *S. aureus*, *E. coli*). There was synergic activity against *E. coli*. This indicates the combination of probiotic strains can be a helpful approach in treating VVIs.<sup>26</sup> These data indicate synbiotics can be helpful in different VVIs and act by different mechanisms.

### Use in Nonpregnant Women

A recent Cochrane systematic review assessed the effectiveness of probiotics for the treatment of VVC in nonpregnant women. Review involved 10 randomized controlled trials (RCTs) ( $n = 1,656$  patients) where probiotics were administered by either oral or vaginal route as an add-on to antifungal drugs. There was slight improvement in the short-term in clinical [risk ratio (RR) 1.14, 95% CI 1.05–1.24] and mycological (RR 1.06, 95% CI 1.02–1.10) cure rate. Probiotics also reduced the relapse rate at 1 month (RR 0.34, 95% CI 0.17–0.68). However, review did not find effect on long-term (3-month posttreatment) clinical (RR 1.30, 95% CI 1.00–1.70) or mycological (RR 1.16, 95% CI 1.00–1.35) cure rate. The quality of RCTs was reported to be low or very low. It emphasizes the need of well-designed RCTs with larger sample size, with a longer follow-up.

Increasing resistance to the azole antifungals poses challenges in the treatment of recurrent VVC. Also, in complicated VVIs, the existing treatments may not be supportive of long-term beneficial results. In these patient subgroups, the use of *Lactobacillus* species-containing probiotics (*L. plantarum* P17630) prevented the

VVC recurrences.<sup>27</sup> Thus, probiotics have a potential for empirical use in treating VVIs.

In patients with BV, various meta-analyses support the beneficial effect of probiotics supplementation. Combined with metronidazole or used alone, a Cochrane review in the year 2009 demonstrated positive results with the use of oral and vaginal probiotics.<sup>28</sup> In 2013, Huang et al. performed a systematic review to assess the effect of probiotics for the treatment of BV. In total, twelve RCTs were included that had a follow-up period ranging from 1 to 6 months. Route of probiotics administration was either oral or vaginal in eight and four studies, respectively. The cure rate of BV was significantly improved (RR 1.53, 95% CI 1.19–1.97) with probiotic supplementation. However, there was a substantial heterogeneity in different studies.<sup>29</sup> In another recent meta-analysis, five RCTs studies ( $n = 1,186$  participants) were included that compared metronidazole alone with the combination metronidazole plus probiotics in the treatment of BV. Compared to metronidazole alone, there was no significant difference in the cure rate with the use of combination of metronidazole and probiotics (risk ratio of 0.98, 95% CI 0.91–1.06;  $p = 0.57$ ).<sup>8</sup> Based on the current evidence, various guidelines recommend the use of probiotics in VVIs as shown in Table 2.<sup>30–34</sup>

### Use in Pregnant Women

In pregnancy, preterm birth is not desirable. Its etiology is multifactorial. Intrauterine inflammation due to ascending vaginal infections is responsible for preterm birth in nearly one-third of cases. In patients with existing BV, preterm birth can occur. Probiotics administration is responsible for the development of antiinflammatory cytokines and vaginal pH reduction. The latter makes the vaginal environment favorable to the healthy microflora. In addition, probiotics administration improves maternal glucidic metabolism and improves insulin sensitivity as well.<sup>35</sup>

Recent meta-analysis evaluated the risk of preterm birth in pregnant women treated with probiotics. A total of 21 studies were included. Preterm birth <34 weeks or birth <37 weeks was assessed in 5 ( $n = 1,017$ ) and 11 ( $n = 2,484$ ) studies. It was found

**Table 3:** Suggested dosage of probiotic for various infections in different female populations

Indication	Dosage	Remarks
Recurrent vulvovaginal infection	1 capsule orally twice a day for 15–60 days	To be added along with the oral and vaginal antibiotic therapy and to be continued even after the completion course of antibiotic therapy especially in patients at high risk of recurrence, i.e., diabetics and immune-compromised patients
Recurrent urinary tract infections	1 capsule orally twice a day for 15–60 days	To be added along with antibiotics and to be continued up to 3 months to prevent further any recurrence
Vaginitis in pregnancy	1 capsule orally twice a day for 2 months	To be used especially in those with recurrent infections, relapses, and previous pregnancy losses
Infertility patients	1 capsule orally twice a day for 2 months	To be started in the peri-conceptual period and especially in cases of unexplained infertility
<i>In-vitro</i> fertility patients	1 capsule orally twice a day for 3 months	To be started at least a fortnight before the start of the IVF cycle and to be continued throughout the duration of the IVF cycle, the luteal phase and the successful pregnancy. Especially recommended in cases of recurrent implantation failure/previous failed IVF cases

that the use of probiotics did not affect the risk of preterm birth before 34 weeks (RR 1.03; 95% CI: 0.29–3.64). Similarly, there was no effect on births before 37 weeks (RR 1.08; 95% CI: 0.71–1.63). In addition, secondary outcomes such as gestational diabetes, PPRM, small for gestational age (SGA), and large for gestational age were not affected by probiotics supplementation. There was significant positive effect on glucose metabolism (insulin resistance and insulin levels). However, in a RCT, Daskalakis et al. showed a beneficial effect in PPRM. Treatment regimen included standard antibiotic treatment alone ( $n = 57$ )/antibiotic prophylaxis ( $n = 59$ ) combined vaginal probiotic supplementation (10 days) or control. Compared to the control group, probiotic supplementation was associated with significantly higher mean GA at birth (35.49 vs 32.53 weeks) and latency period (5.60 vs 2.48 weeks).<sup>36</sup> In another study by Neri et al. effects of probiotic-containing yoghurt were assessed in women having BV during the first trimester of pregnancy. Three treatment groups included as Group I (tampon containing 5% acetic acid, inserted twice a day,  $n = 32$ ), Group II (10–15 mL vaginal douche containing  $>1.0 \times 10^8$  colony-forming units/mL of *L. acidophilus*, performed twice a day,  $n = 32$ ), or Group III (no treatment,  $n = 20$ ). Treatments were continued for 1 week. The outcome of treatment was assessed with Amsel criteria. It incorporates three of five findings: (1) amine fishy odor, (2) amine odor with the addition of 10% KOH, (3) vaginal pH  $>4.5$ , (4) clue cells in the vaginal fluid, and (5) milky homogeneous vaginal discharge. At the end of 30 days, Amsel criteria was absent in 88% who received intravaginal Lactobacilli, 38% treated with acetic acid tampons, and 15% receiving the placebo. Compared to placebo, the cure rate of BV was a significant higher with probiotic ( $p < 0.005$ ), and Lactobacilli and acetic acid groups ( $p = 0.004$ ).<sup>37</sup>

## DISCUSSION

The currently available evidence indicates that synbiotics are useful in different VVIs in both pregnant and nonpregnant women. Combination of various Lactobacilli can be useful in improving the clinical, bacteriological/mycological cure rates and prevent the recurrences. The inherent ability of various Lactobacilli in terms of immunomodulation and local pH maintenance is useful in the effective management of VVIs. In different female

population, probiotics can be used in different infections. Based on our experience with the use of probiotics, we advise their use in different women with VVIs. Table 3 shows the current possible indications along with dosage of probiotic and prebiotic combination to be used for effective relief in VVIs.

## CLINICAL SIGNIFICANCE

Vulvovaginal infections (VVIs) are associated with dysregulation of intravaginal microbiome environment. Upregulating this microflora environment with the use of pre- and probiotics is associated with increased rates of treatment success and prevention of recurrences of VVIs. Current evidence indicates beneficial effects with the use of synbiotic treatments in VVIs. Further research should focus on better-quality studies in establishing the definitive role of synbiotic in different VVIs in both pregnant and nonpregnant females.

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