

## Probiotics for woman's health focus on urogenital infections and reproductive outcomes

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### ABSTRACT

Depletion in vaginal *Lactobacilli* colonization is associated with poor urogenital health and adverse pregnancy outcomes. Probiotic supplements containing lactobacilli, when administered in adequate amounts, increased vaginal and gut colonization of *Lactobacilli*, reduced the incidence of bacterial vaginosis and other urogenital infections. Probiotic *Lactobacilli* reduced preterm births and improved fertility rates in women following in vitro fertilization. Probiotics may also improve implantation rate and live-birth rate in women undergoing IVF. The purpose of this review was to critically analyse the available literature for synthesizing evidence on the use of probiotics and its effect on urogenital and reproductive health in women.

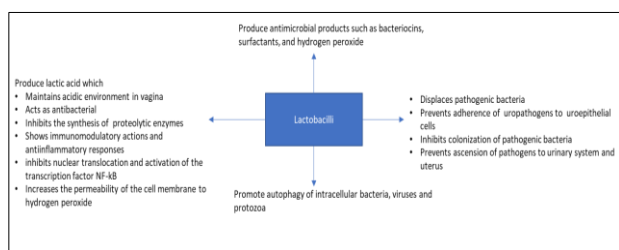
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### INTRODUCTION

The vaginal ecosystem harbours numerous bacterial species and other microorganisms and is referred to as vaginal microbiome. Vaginal microbiome plays a crucial role in maintaining the homeostasis of urogenital tract. The composition of the vaginal microbiome is influenced by genes, ethnic background, and environmental and behavioral factors.<sup>1,2</sup> A healthy vaginal microbiota is dominated by *Lactobacilli* species which owing to their multiple protective mechanisms prevent the growth of pathogenic microorganisms. However, under certain

conditions there is reduction in the vaginal *Lactobacilli* count which promotes the growth of pathogenic microbes. This dysbiosis in the vaginal microbiota increases susceptibility of the host to several urogenital and sexually transmitted diseases. Vaginal dysbiosis is also associated with infertility, adverse reproductive outcomes, and poor clinical outcomes in women undergoing invitro fertilization (IVF). Available evidence suggests that probiotic *Lactobacilli* are capable of restoring the vaginal eubiosis and can be used as adjuvant therapy in the management of urogenital infections and for improving pregnancy outcomes.<sup>1,2</sup> The present review

focuses on the impact of vaginal dysbiosis on the reproductive health and the use of probiotic *Lactobacilli* in prevention and treatment of bacterial vaginosis and improving pregnancy outcomes.



**Figure 1: Pleiotropic effects of lactobacillus.**

### ***Vaginal dysbiosis linked to urogenital infections***

In healthy women, the vaginal microbiome is dominated by *Lactobacilli* which comprise 90 to 95% of the total bacterial count of the reproductive system.<sup>1</sup> The *Lactobacilli* play an important role in providing protection against invasion and colonization by opportunistic pathogens. Several mechanisms have been proposed to explain the protective effects of *Lactobacilli* which include production of lactic acid, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), antimicrobial peptides, and biosurfactants, promotion of autophagy, and competitively inhibiting the attachment of other microbes to vaginal epithelial cells (Figure 1).<sup>2-4</sup> *Lactobacilli* produce lactic acid which maintains the acidic pH of the vaginal mucosa. The acidic environment of the vagina inhibits the growth and colonization of pathogenic microbes.<sup>2</sup> Moreover, *Lactobacilli* provide a physical barrier which prevents the colonization of pathogenic organisms in the vagina and reduces the ascension of pathogens to urinary tract which may confer protection against urinary tract infections (UTIs).<sup>2-4</sup> However, depletion of *Lactobacilli* can occur in the vaginal mucosa under the influence of some intrinsic and extrinsic factors. Vaginal dysbiosis is associated with increased risk of bacterial vaginosis and other infections such as trichomonas vaginalis, neisseria gonorrhoeae, chlamydia trachomatis, herpes simplex virus (HSV), human papillomavirus (HPV), and Human immunodeficiency virus (HIV).<sup>2</sup>

### ***Oral probiotics for bacterial vaginosis***

Bacterial vaginosis is the most common vaginal infection in women of reproductive age. Bacterial vaginosis occurs due to depletion of *Lactobacilli* which facilitates the colonization of anaerobic bacteria particularly *G. vaginalis*, *Megasphaera*, and *Eggerthella*. Although antibiotics are recommended for the management of bacterial vaginosis treatment, use of antibiotics is associated with adverse effects and high recurrence rates. Moreover, antibiotics may also suppress the growth of *Lactobacilli* which antagonize the colonization of pathogens causing bacterial vaginosis. Further, bacteria

within the biofilm are less exposed to antibiotics and hence, develop resistance quickly. Biofilms persist for a longer period which leads to relapse or recurrence of bacterial vaginosis. Considering these limitations, *Lactobacilli*-based probiotics have been proposed as an alternative option in the management of bacterial vaginosis.<sup>5-8</sup> Available evidence suggests that certain strains of *Lactobacilli* when administered orally or vaginally can colonize the vagina and restore the balance of vaginal microbiome and reduce the risk of bacterial vaginosis.

Although it is unclear as to which route is more efficient, oral route is preferred over vaginal route as oral formulations are easy to administer.<sup>6,8-11</sup> When taken orally, *Lactobacilli* migrate from the intestine to vaginal mucosa through rectum and valvular skin.<sup>11</sup> In addition to their inhibitory actions on the growth and colonization of pathogenic microbes, *Lactobacilli* can disrupt bacterial biofilms by incorporating themselves into the biofilms.<sup>8</sup> Further, long-term administration of probiotics does not cause adverse reactions and can be considered for reducing the recurrence of bacterial vaginosis.<sup>6,8</sup> Reid et al, reported that when administered orally, probiotics restored the normal vaginal flora, depletion of vaginal yeast count and decreased the count of coliforms significantly.<sup>12</sup> In a randomized controlled trial (RCT), Anukam et al, evaluated the efficacy of augmentation of oral metronidazole with oral probiotics in women with Bacterial vaginosis.<sup>13</sup> The authors randomized metronidazole-treated patients to twice daily oral probiotics or placebo for 30 days. The authors concluded that augmentation of antibiotic with probiotic produced higher cure rate than treatment with antibiotic alone (88% versus 40%).<sup>13</sup> A cochrane review found that metronidazole/probiotic preparation is beneficial and appear promising in producing microbiological cure and symptom resolution in bacterial vaginosis, but well-designed randomized controlled trials with standardized methodologies and larger patient size are needed.<sup>7</sup> Vigneshwari et al, assessed the efficacy of probiotics as a supplement along with metronidazole in treatment of bacterial vaginosis in Indian women of reproductive age. The authors reported a higher reduction in Nugent score in patients treated with probiotics plus metronidazole than in patients treated with metronidazole alone.<sup>14</sup> In a recent multicenter RCT, Heczko et al, evaluated the efficacy of oral probiotic preparation with standard antibiotic therapy in reducing the recurrence of bacterial vaginosis and aerobic vaginitis.<sup>15</sup> The authors randomized women aged between 18 to 58 years with histories of recurrent bacterial vaginosis or aerobic vaginitis to receive metronidazole or standard antibiotic therapy (in case of failure of metronidazole therapy) and probiotic or placebo. Probiotic supplementation significantly lengthened the time to relapse of bacterial vaginosis or aerobic vaginitis compared to placebo. The relapse of bacterial vaginosis was lengthened by as much as 76% in patients receiving probiotics. In addition, improvement in clinical symptoms, reduction in Nugent score, and

increase in the vaginal *Lactobacilli* count was also reported in the probiotic group.<sup>15</sup> A list of studies that evaluated the efficacy oral probiotics in bacterial vaginosis is given in Table 1.

### Abnormal vaginal microbiome and reproductive outcomes

Aberrant vaginal microbiome with diminished *Lactobacilli* dominance is associated with poor reproductive outcomes. Dysbiotic vaginal microbiome during gestation is associated with increased pregnancy loss (at 10-16 weeks) in spontaneous pregnancies and early pregnancy loss (before 6 weeks) after invitro

fertilization (IVF). Abnormal vaginal microbiome is also associated with poor clinical pregnancy rates in women following IVF.<sup>1,18,19</sup>

Bacterial vaginosis which is a direct consequence of depletion in vaginal *Lactobacilli* is linked to infertility and adverse clinical outcomes in women. Therefore, an increase in *Lactobacilli* colonization and a decrease in bacterial vaginosis- causing pathogen count may have a positive influence on the pregnancy outcomes. It is evident from the available literature that oral administration of *Lactobacilli*-based probiotics improved the Nugent score and reduced the number of pathogenic bacteria in women with bacterial vaginosis.<sup>12-17</sup>

**Table 1: Studies evaluating efficacy of oral probiotics in bacterial vaginosis.**

Interventions	Patient population	Duration of the study	Outcomes	Reference
<i>L. rhamnosus</i> GR-1 and <i>L. fermentum</i> RC-14 or placebo	Healthy women (mean age 35 years)	60 days	<i>Lactobacilli</i> were detected in more women in the <i>lactobacilli</i> -treated group than in the placebo group at 28-day (P = 0.08) and 60-day (P = 0.05) test points.	Reid G et al <sup>12</sup>
<i>L. reuteri</i> RC-14, and <i>L. rhamnosus</i> GR-1 plus metronidazole or placebo plus metronidazole	Women (18-48 years) with BV	Antibiotic treatment was given for 7 days. Probiotics were given for 30 days	Cure rates: 88% in antibiotic plus probiotic group; 40% in antibiotic plus placebo group	Anukam K et al <sup>13</sup>
<i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 (2 capsules) or placebo plus tinidazole	Women (16-51 years) with BV	4 weeks	Cure rate: Significantly higher in probiotic group than antibiotic (placebo) alone group (87.5% versus 50%; P = 0.001) At the end of treatment, the proportion of women with normal vaginal microbiota were twice higher in the probiotic group compared to placebo group (75.0% versus 34.4%; P = 0.011)	Martinez RC et al <sup>16</sup>
<i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 or placebo	Adult women with vaginal infection (BV, candidiasis, trichomoniasis or combination of these conditions)	6 weeks	Normal vaginal microbiota was restored in 61.5% of patients receiving probiotics compared to 26.9% in the placebo group	Vujic G et al <sup>17</sup>
<i>L. rhamnosus</i> and <i>L. reuteri</i> plus metronidazole versus only metronidazole	Adult women with BV	7 days	Higher reduction in Nugent score was reported in patients treated with probiotic plus metronidazole	Vigneshwari et al <sup>14</sup>
Mixture of <i>L. gasseri</i> 57C, <i>L. fermentum</i> 57A, and <i>L. plantarum</i> 57B versus placebo along with metronidazole or standard antibiotic therapy	Adult women with history of recurrent BV or AV	10 days	Treatment with probiotic significantly lengthened the time to relapse of BV or AV clinical symptoms compared to placebo Treatment with probiotics lengthened the time to relapse of BV by as much as 76 %, reduced the Nugent score, maintained vaginal pH, and stimulated an increase in the <i>Lactobacilli</i> count	Heczko et al <sup>15</sup>

AV: Aerobic vaginitis, BV: Bacterial vaginosis.

### ***Bacterial vaginosis is associated with infertility and poor pregnancy outcomes***

Bacterial vaginosis is associated with increased risk of sexually transmitted diseases, pelvic inflammatory diseases, endometritis, UTIs, and infertility.<sup>5,18,20,21</sup> In infertile women, the prevalence of bacterial vaginosis was found to be 19% whereas the prevalence of abnormal microflora including bacterial vaginosis and intermediate microflora was reported to be 39%.<sup>20</sup> Bacterial vaginosis increases the risk of anovulation, early and preclinical pregnancy loss following IVF, preterm premature rupture of membranes, amniotic fluid infection, intrauterine infection, preterm labour, and perinatal infections.<sup>5,6,19-21</sup>

Bacterial vaginosis was found to be three times more prevalent in infertile women compared to antenatal women (OR 3.32; 95% CI 1.53-7.20).<sup>20</sup> Tubal infertility is a leading cause of infertility. Pelvic inflammatory diseases (PID) and bacterial vaginosis are considered as the main causative factors for tubal infertility. The risk of future tubal factor infertility was found to increase with each episode of PID.<sup>22</sup> Haggerty et al, reported that the women who tested positive for bacterial vaginosis-causing bacteria in the cervix and/or endometrium were three times more likely to experience infertility.<sup>23</sup> Among infertile women, the prevalence of bacterial vaginosis was twice higher in women with tubal infertility compared to women with other causes of infertility (OR 2.77; 95% CI 1.62-4.75).<sup>20</sup> A recent meta-analysis reported that the tubal infertility was significantly more prevalent in patients with bacterial vaginosis compared to patients with normal vaginal microbiota (45% versus 28%;  $P < 0.001$ ).<sup>24</sup> Based on the available evidence, probiotics can be used to treat bacterial vaginosis and restore and maintain a healthy vaginal ecosystem which may improve reproductive outcomes.

### ***Probiotics and preterm delivery***

Colonization of the genital tract by pathogenic organisms during pregnancy can trigger inflammatory cascade and release of proteolytic enzymes such as matrix metalloproteinases (MMPs), elastase, mucinase, and collagenase.<sup>25,26</sup> These enzymes stimulate the degradation of mucosal epithelial barrier and cervical plug which compromises the protective barrier mechanism.<sup>26</sup> As a result, the infection spreads to uterine cavity and compromise the integrity of the foetal membranes. Bacterial colonization in the amniotic cavity activates the innate immune system and stimulates the production of prostaglandins, leading to intrauterine contractility and increased risk of preterm labour.<sup>25-27</sup>

*Lactobacilli* can prevent the degradation of cervical tissue by inhibiting the colonization of pathogenic bacteria and release of MMP-8 which reduces the ascension of pathogens to uterine region and microbial invasion of the amniotic cavity. In addition, *Lactobacilli* possess anti-inflammatory and immunomodulatory properties and can

reduce systemic inflammation which plays a central role in the cascade of events that lead to preterm labor.<sup>2,27</sup> The association between intake of probiotic *Lactobacilli* and reduction in risk of preterm delivery was established in clinical studies.<sup>28,29</sup> Myhre et al, reported that the intake of probiotics reduced the risk of preterm labor by 18% (OR 0.82; 95% CI 0.681-0.986;  $p = 0.035$ ). However, the study was based on the use of recall questionnaires and there was a lack of clarity in reporting outcomes.<sup>28</sup> Nordqvist conducted a prospective observational cohort study to evaluate the effect of probiotic *Lactobacilli* (milk product) on the risk of preterm delivery in 37050 nulliparous women. The authors found that consumption of probiotic product during early pregnancy reduced the risk of preterm delivery by 21% (OR 0.79; CI 0.64-0.97).<sup>29</sup>

### ***Abnormal vaginal microbiome and IVF outcomes***

A high prevalence of bacterial vaginosis and abnormal vaginal microbiome was reported in IVF patients. Bacterial vaginosis is associated with tubal infertility and miscarriage in women following IVF and may negatively affect the clinical pregnancy rate in IVF patients.<sup>19,20</sup> In infertile women, bacterial vaginosis doubles the risk of early pregnancy loss after established pregnancy following IVF treatment (OR 2.36; 95% CI 1.24-4.51).<sup>20</sup> In addition, the risk of early spontaneous abortion rate was found to be 68% higher in bacterial vaginosis-positive IVF patients compared to patient's normal vaginal microbiota (RR 1.68; 95% CI 1.24-2.27;  $I^2 = 0\%$ ).<sup>24</sup> Moreover, the presence of pathogenic cervical microorganisms significantly lowered clinical pregnancy rates, ongoing pregnancy rates, and implantation rates in women undergoing ovarian stimulation for IVF-embryo transfer.<sup>30</sup>

Several authors studied the role of microbial infection on the outcome of IVF-ET treatment. One study reported that in patient undergoing IVF, pregnancy rates were significantly lower in patients testing positive for *Enetrobacteriaceae* and *Staphylococcus* species than those in the negative culture group.<sup>31</sup> Maduka and colleagues conducted an analytical cross-sectional study among women undergoing IVF-ET treatment to assess the effect of bacterial colonization of the ET catheter tip on the clinical pregnancy rate.<sup>32</sup> The authors found that bacterial colonization of the ET catheter tip was associated with a reduction in the clinical pregnancy rate.<sup>32</sup> The predominant pathogens isolated from the ET tip in these studies were *E. coli*, *Staphylococcus* and *Streptococcus* species.<sup>31,32</sup>

Moore et al, reported significantly lower live-birth rates when Viridans S was recovered from the embryo transfer catheter tip than when it was not (6% versus 35%,  $p = 0.04$ ).<sup>33</sup> In fact, a 50% reduction in pregnancy rate was reported when pathogenic bacteria were recovered from the embryo transfer-catheter tip in several studies.<sup>33</sup> Using a metagenomics approach, Hyman et al, reported

that there is a shift in the vaginal microbiome during IVF-ET therapy.<sup>34</sup> The authors found that the pregnancy outcomes are influenced by the vaginal microbiome on the day of embryo transfer and a vaginal microbiome composed solely of *Lactobacilli* is crucial for a favourable outcome of the IVF-ET procedure. Moreover, women with a non-*Lactobacilli*-dominated microbiota and a receptive endometrium had a significantly lower rate of implantation, pregnancy, and live birth than patients with a *Lactobacilli*-dominated microbiota.<sup>34</sup>

In infertile patients undergoing IVF, the presence of a non-*Lactobacilli*-dominated microbiota in a receptive endometrium was associated with significant decrease in implantation (60.7% versus 23.1%;  $p = 0.02$ ), pregnancy (70.6% versus 33.3%  $p = 0.03$ ), ongoing pregnancy (58.8% versus 13.3%,  $p = 0.02$ ), and live birth (58.8% versus 6.7%,  $p = 0.002$ ) rates.<sup>18</sup> These adverse effects were more evident in subjects presenting with high percentages of *Gardnerella* and *Streptococcus* species.<sup>18</sup> On the contrary, the live-birth rate was thrice higher when H<sub>2</sub>O<sub>2</sub>-producing *Lactobacilli* (without *S. Viridans*) was isolated from the ET catheter tip than when no bacteria were isolated from the catheter tip (88% vs. 26%,  $p = 0.003$ ).<sup>33</sup> Similarly, live-birth rate was more than twice higher when H<sub>2</sub>O<sub>2</sub>-producing *Lactobacilli* was recovered from the vagina at ET (50%) than when it was not (50% versus 21%;  $P = 0.01$ ).<sup>33</sup>

The infection of the endometrial lining by the varying species of microbiome produces chronic endometritis. Approximately 45% of infertile population may be affected by chronic endometritis and this percentage can be higher as these patients mostly are asymptomatic and do not show much change on ultrasound. They can benefit from probiotics and antibiotic course which would decrease the chances of RIF (recurrent implantation failure) in ART and recurrent pregnancy loss (RPL).<sup>35</sup>

Endometriosis affects 10% of the reproductive age women wherein there is presence of ectopic endometrial tissue apart from the uterine lining. The cause of endometriosis is unknown. Khan et al, compared the endometrial samples of endometriosis and control group and found that there were reduced *Lactobacilli* in endometriosis group. They suggested that dysbiosis of the uterine microbiome could be a cause of endometriosis.<sup>36</sup>

Kamala et al, reported that pregnant women (following IVF procedure) with bad obstetric history treated with probiotics had higher rates of delivery and lower rates of fetal loss compared to those not treated with probiotics (delivery rates: 80% versus 63%).<sup>37</sup> Using backward conditional logistic regression analysis, the authors found that probiotic treatment as significant factor which is responsible for pregnancy outcome (Adjusted OR 2.721; 95% CI 1.232-6.011).<sup>37</sup> These findings suggest that there may be a window of opportunity for improving IVF reproductive outcomes by identifying high risk women

with abnormal vaginal microbiome including bacterial vaginosis and treating them well in advance.<sup>38-40</sup> Such high-risk category may also include women with history of pelvic inflammatory disease (PID). Moreover, findings emphasize the importance of the assessment of the reproductive tract microbiome during IVF procedures to prevent adverse reproductive outcomes. Hence clinicians should follow a “screen and treat approach” to avoid adverse reproductive outcomes in patients undergoing IVF.

## CONCLUSION

A healthy vaginal microbiome dominated by *Lactobacilli* species is essential for urogenital and reproductive health. A depletion in *Lactobacilli* increases the risk of bacterial vaginosis and adversely affects fertility rates and birth rates. The presence of pathogenic bacteria on the catheter tip adversely affects pregnancy outcomes in women undergoing IVF. Oral supplementation of probiotic *Lactobacilli* restores the normal balance of the urogenital microbiota which reduces the colonization of pathogenic bacteria and prevents their ascension. Based on the available evidence, probiotics may be considered as alternative means for improving urogenital health and reproductive outcomes in women. However, a carefully designed clinical trial using well characterized probiotic strains and treatment regimens to evaluate the effect of probiotics on IVF embryo transfer and pregnancy rates are needed.

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