

Ingestion of Probiotics: Optional Treatment of Bacterial Vaginosis in Pregnancy

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For Editorial see page 374

Bacterial vaginosis is the primary cause of abnormal vaginal discharge in women of reproductive age. In epidemiologic studies of women with vaginitis, at least 30 to 50% of all women have BV. The predominant bacteria in the normal vaginal flora are *Lactobacillus* species, which establish a low vaginal pH by producing lactic acid. Some types of *Lactobacillus* also generate hydrogen peroxide. The low pH value and the presence of hydrogen peroxide inhibit the growth of most other microorganisms.

In women with BV, the vaginal flora are altered by replacement of the normal peroxide-producing *Lactobacillus* species with high concentrations of anaerobic bacteria (e.g., *Mobiluncus* sp. *Bacteroides* sp.), *Gardnerella vaginalis*, and *Mycoplasma hominis* [1,2]. Although BV is the most prevalent cause of vaginal discharge or mal-odor; half of the women who meet the clinical diagnostic criteria for BV are asymptomatic.

Diagnosis of BV

The clinical diagnosis of bacterial vaginosis requires at least three of the following four criteria [3]: a) a thin, homogeneous, white discharge often adhering to the vaginal walls, b) the presence of clue cells (>20% of epithelial cells) on microscopic examination, c) a pH less than 4.5 in vaginal fluid, and d) a fishy odor before or after adding 10% KOH (whiff test).

A Gram stain of vaginal secretion is another accepted method for diagnosing BV. The stain reveals loss of *Lactobacillus* morphotypes and an increase in *Gardnerella* and *Bacteroides* morphotypes and curved gram-variable rods. Based on the standard criteria, the specificity and sensitivity of the Gram stain for diagnosis of BV is 83% and 89% respectively [4]

Treatment of BV

Metronidazol and clindamycin were both found to be effective for treating BV [5]. Both drugs are presented in two forms – either tablets for oral use, or cream or gel for local application. Several regimens are available. In the *Morbidity and Mortality Weekly Report*, in the 1998 guidelines for the treatment of sexually transmitted diseases, the Centers for Disease Control recommended regimens

for non-pregnant women [6] [Table 1]. In addition, patients should be advised to avoid consuming alcohol during treatment with metronidazol and 24 hours thereafter. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms. An alternative regimen, which has lower efficacy, is metronidazol 2 g orally in a single dose. Clindamycin 300 mg orally twice a day for 7 days is an additional alternative regimen [6]. The possible side effects of metronidazol taken orally are mainly gastrointestinal, including nausea, vomiting, abdominal cramping, and an unpleasant metallic taste. Peripheral neuropathy has been reported mainly with prolonged therapy. Clindamycin may cause nausea, vomiting, diarrhea, and a skin rash. Clindamycin may also cause pseudomembranous colitis. Both metronidazol and clindamycin have limited systemic absorption following topical application; nevertheless, topical medication can also be responsible for the same side effects.

Bacterial vaginosis in pregnancy

Various gynecologic and obstetric conditions are clinically associated with bacterial vaginosis. BV was found in 15–23% of pregnant women, half of whom were asymptomatic [7]. Pregnant women with BV are considered to be at increased risk for preterm birth, infants with low birth weight, premature rupture of the membranes, chorioamnionitis, and post-cesarean section and postpartum endometritis. A positive association between spontaneous preterm delivery and BV was found with relative risks varying from 1.5 to 4 [6,8,9].

Table 1. The Centers for Disease Control (MMWR) guidelines for general treatment of BV and in pregnant women [6]

Drug	Regimen	During pregnancy
Metronidazol	Tablet, 500 mg orally 3 times daily for 7 days	Tablet, 250 mg orally 3 times daily for 7 days
	or Gel 0.75%, one applicator (5 g) intravaginally 3 times daily for 5 days	or Tablet, 500 mg x4 (2 g) orally in single dose or Gel 0.75%, one applicator (5 g) intravaginally 3 times daily for 5 days
Clindamycin	Cream 2%, one applicator (5 g) intravaginally at bedtime for 7 days	Tablet, 300 mg orally twice daily for 7 days

BV = bacterial vaginosis

These observations are not at all surprising. It is well accepted that chorioamnionitis is strongly correlated with preterm delivery [10]. Preterm labor and preterm premature rupture of the membranes are frequently accompanied by evidence of infection, manifested by the presence in the amniotic fluid of organisms or inflammatory cytokines [11,12]. Most of these microorganisms are thought to come from the vagina, especially among women with bacterial vaginosis [12]. Mechanisms that may initiate preterm birth in these circumstances are not fully understood. Bacteria may induce prostaglandin synthesis in amniotic cells via several means. Many genital tract organisms associated with BV (but not *Lactobacillus*) synthesize phospholipase A2, an enzyme that liberates arachidonic acid. Bacteria may induce prostaglandin synthesis via direct invasion of the extraplacental membranes, which could lead to disruption of the amniotic cells and release of lysosomal phospholipase. A third possible mechanism that may initiate labor is the migration of maternal inflammatory cells that do metabolize arachidonic acid. Interleukins 1 and 6 and tumor necrosis factor – macrophage secretory products that are found in large quantities in infected amniotic fluid – have been implicated in prostaglandin synthesis and labor. Finally, many of the *Bacteroides* species that produce protease, together with other microorganisms that produce collagenase, bring about a reduction in the strength and elasticity of the amniochorion membranes [7].

A recent study [13] found that pregnant women who have BV at the time of recruitment were nearly twice as likely to have a detectable level of vaginal fibronectin compared with women without BV. In previous studies, detection of cervicovaginal fetal fibronectin early in the third trimester was associated with a risk of preterm delivery, which increased up to almost 4 to 9 times among unselected cohorts and up to 3.6–20.9 among women with symptoms of preterm labor or preterm premature rupture of the membranes. Interestingly, in the aforementioned study [13], women with BV who smoked at the time of recruitment were nearly eight times as likely to have a detectable level of vaginal fibronectin compared with smoking women without BV. Cervical lactoferrin (an iron-binding glycoprotein) concentration was also strongly related to bacterial vaginosis [14]. Lactoferrin levels are known to increase in preterm labor with an amniotic fluid infection. Preterm birth is accepted as a common and the most important cause of neonatal morbidity and mortality. Therefore, reducing the rate of this complication will save lives and eliminate morbidity.

In the United States, BV affects approximately 800,000 pregnant women per year. It has been claimed that if treating BV were to reduce this risk, as many as 80,000 preterm births, leading to 4,000 perinatal deaths and 4,000 infants with neurologic abnormalities, might be prevented each year [5].

Treatment of BV in pregnancy

Pregnant women with symptomatic BV should definitely be treated to relieve symptoms, regardless of a lack of history of previous preterm birth or premature preterm rupture of the membranes. A meta-analysis [15] suggests that metronidazol in pregnant patients is not associated with increased teratogenic risk; nevertheless,

lower doses of the drug are recommended to minimize exposure to the fetus [Table 1].

Whether pregnant women with asymptomatic BV should be treated is still controversial. In a prospective study of cohorts of low risk pregnant women, the finding of asymptomatic BV was not associated with an increase in preterm birth rate [16]. Several randomized prospective studies examined the effect of treatment for BV on adverse outcome of pregnancy [5,17–24]. The studies used different treatment regimens. Starting time ranged from 14 to 24 weeks gestational age. Doses of metronidazol were reduced to a maximum of 750 mg per day given up to 7 days [18–20], or in two doses of 2 g [5], and in one study erythromycin was added [20]. Clindamycin, when used, was applied intravaginally, 2% 5 g at bedtime for 7 days [21,22]. In other studies, 600–900 mg were used orally for 4–7 days [23,24]. It must be stressed that in some of the studies the sample size was small and often no distinction was made between symptomatic and asymptomatic patients. In some studies the population comprised low risk pregnant woman [5,19,21,22,24], while in others they had a history of preterm birth [5,18,20,23,24]. Clearly, the effects of the various treatments differed, with two studies [22,24] showing a reduction in preterm deliveries in the population at low risk, and others demonstrating no effect [5,19,21]. The benefit of the treatment was observed in three studies of a high risk population [18–20], but no effect could be demonstrated in the rest [5,21–24]. In the largest, most recent randomized controlled study, no effect could be found for metronidazol in either low or high risk pregnant women [5]. The recommend approach in pregnancy is to treat the symptomatic patient, to screen the high risk population and to treat the asymptomatic BV women at high risk [17].

Probiotic bacteria

In 1989 probiotic was defined as “live microbial feed supplement, which beneficially affects the host animal by improving its intestinal microbial balance” [25]. This definition was broadened 3 years later to a “mono- or mixed-culture of live microorganisms which benefits man or animals by improving the properties of the indigenous micro flora” [26]. The definition was further refined in 1998 to “living microorganisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition” [27].

The lactobacilli are gram-positive non-pore-forming facultative or anaerobic rods. These organisms utilize carbohydrates, and the main product of the glucose fermentation is lactic acid. Besides lactic acid, lactobacilli also produce acetic acid and hydrogen peroxide, making the environment less favorable for *in vitro* growth of potentially pathogenic microorganisms. Lactobacilli constitute the majority of vaginal microflora during birth and about 25 hours after birth. The colonic microflora primarily consist of lactobacilli and bifidobacteria [28]. Evidence has accumulated proving that administration of selected microorganisms including non-pathogenic yeast and several genera of bacteria, such as lactobacilli and bifidobacteria, is beneficial in the prevention and treatment of certain intestinal infections and possibly also vaginal infection [29].

The concept that lactobacilli might be useful in displacing and replacing harmful microorganisms on mucosal surfaces dates back

to Elie Metchnikoff in 1908 [30]. Following anecdotal reports, Hilton et al. [31] in 1992 were the first to perform a controlled crossover study to examine whether daily ingestion of yogurt containing *Lactobacillus acidophilus* prevents vulvovaginal candidal infection. They found that daily ingestion of 8 ounces of yogurt containing *L. acidophilus* decreased candidal colonization and infection. This study was criticized for several reasons. Previous *in vitro* studies examining the adherence of *Lactobacillus* sp. to normal human vaginal epithelial cells found that *L. acidophilus* isolated from yogurt showed a significantly lower adherence than did other *Lactobacillus* species; thus, commercial yogurt may not be a reliable way to deliver lactobacilli [32]. Furthermore, the study lacked a control with pasteurized yogurt. Finally, the patients used *Lactobacillus*-containing preparations, often in preference to topical antifungal agents. The editorial comment on the study concluded that the true value of this approach warrants further analysis [33].

Probiotic bacteria and BV

Lactobacilli have long been thought to protect against vaginal infections by maintaining an acid environment or by producing metabolites, such as hydrogen peroxide, that inhibit other vaginal microorganisms [2]. However, only a few examined the effect of probiotics for treatment of BV. In a letter to *The Lancet* in 1987, Fredricsson et al. [34] presented clinical evidence that intravaginal application of yogurt for the treatment of BV is rarely effective.

Neri and colleagues [35] were the first to achieve favorable results by using intravaginal applications of yogurt to treat 32 women with BV in the first trimester of pregnancy. The results indicated that the continuous correction of vaginal pH and *Lactobacillus* flora is crucial for normal vaginal ecology. In a controlled crossover study, Shalev et al. [36] treated 46 women suffering from BV. Twenty-three women began eating yogurt that contained *Lactobacillus*, while the other 23 began eating a pasteurized yogurt. When yogurt that contained *L. acidophilus* was consumed there was a significant increase in the number of positive vaginal cultures with *L. acidophilus* ($P=0.001$) and a significant reduction in the number of episodes of BV during that time ($P<0.001$). It has been suggested that the survival of *L. acidophilus* is improved on passage through the gastrointestinal tract compared with other *Lactobacillus* species [37].

In conclusion, the possibility of using lactobacilli is promising. Although scientific confirmation is still needed, probiotics may be especially important for reducing the preterm birth rate in pregnant women. It has been claimed that intrauterine infection with BV may antedate the pregnancy [38]. Probiotics can safely be used before pregnancy or in the first trimester. Moreover, it may be used as an adjunctive to therapy in the second trimester, avoiding potential side effects and teratogenicity of standard treatments. Probiotics may well be the answer.

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