

INGESTION OF PROBIOTICS, OPTIONAL TREATMENT OF BACTERIAL VAGINOSIS IN PREGNANCY

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Bacterial Vaginosis

Bacterial vaginosis (BV) is the primary cause of abnormal vaginal discharge in women of reproductive age. In epidemiological 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. The *Lactobacillus* establishes 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 is altered by replacement of the normal peroxide-producing *Lactobacillus* species with high concentration of anaerobic bacteria (e.g., *Mobiluncus* sp., *Bacteroides* sp.), *Gardenerella* vaginitis and *Mycoplasma hominis*^{1,2}.

Although BV is the most prevalent cause of vaginal discharge or malodor, 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 criteria³. A thin, homogeneous, white discharge often adheres to the vaginal walls; presence of clue cells (>20% of epithelial cells) on microscopic exam; pH of vaginal fluid of > 4.5; a fishy odor before or after adding 10% KOH (whiff test).

A Gram stain of vaginal secretion is an accepted additional diagnostic test of BV. The stain reveals loss of *Lactobacillus* morphotypes and an increase in *Gardenerella* 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 were 83% and 89% respectively⁴.

Treatment of BV

Metronidazol and Clindamycin were both found to be effective in treating BV¹⁴. Both drugs are presented in two forms – either tablets for oral use or cream or gel

for local application. Several regimens are available. The CDC in the Morbidity and Mortality Weekly Report (MMWR) in the 1998 guidelines for treatment of Sexually Transmitted Diseases has recommended the following regimens for non pregnant women: Metronidazol 500 mg orally twice a day for 7 days; or Clindamycin cream 2%, one full applicator (5 g) intravaginally at bed time for 7 days; or Metronidazol gel 0.75%, one full applicator (5 g) intravaginally twice a day for 5 days.

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 a 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 regimen⁶.

With oral use the possible side effects of metronidazol are mainly gastrointestinal, including nausea, vomiting, abdominal cramping and an unpleasant metallic taste. Peripheral neuropathy has been reported mainly with prolonged therapy. Clindamycin can be responsible for 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 gynecological and obstetrical conditions are clinically associated with Bacterial Vaginosis. BV was found in 15 to 23 percent of pregnant women, half of them were asymptomatic⁵. Pregnant women with BV are considered to be at increased risk for having preterm birth, infants with low birth weight, premature rupture of the membranes, chorioamnionitis, and post-cesarean section and postpartum endometritis. Positive association between spontaneous preterm delivery and BV was found with relative risks varying from 1.5 to 4⁶⁻⁸.

These observations are not at all surprising. It is well accepted that chorioamnionitis is strongly correlated with preterm delivery⁹. 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^{10,11}. Most of these microorganisms are thought to come from the vagina, especially among women with bacterial vaginosis¹¹. Mechanisms that may initiate preterm birth in these circumstances are not fully understood. Bacteria may induce prostaglandin synthesis in amniotic cells via several ways. 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 that will 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, which metabolize arachidonic acid.

Interleukins 1 and 6 and tumor necrosis factor, which are macrophages secretory products and are found in large quantity in infected amniotic fluid, have been implicated in prostaglandin synthesis and labor. Finally, many of the Bacteroides species produce protease and other microorganisms produce collagenase that reduce the strength and elasticity of the amniochorion membranes⁵.

In a recent study, it was found that pregnant women who have BV at the time of recruitment were nearly two times 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 has been associated with a risk of preterm delivery increased up to nearly 4-9 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 recent study it was found that women who have BV and 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 BV¹². Cervical Lactoferrin (an iron binding glycoprotein) concentration was also strongly related to bacterial vaginosis¹³. 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 much morbidity.

In the United States BV affects approximately 800,000 pregnant women per year. It has been claimed that if the treatment of BV were to reduce this risk, as many as 80,000 preterm births, leading to 4000 perinatal deaths and 4000 infants with neurological abnormalities might be prevented per year¹⁴.

Treatment of BV in Pregnancy

Pregnant women who have symptomatic BV should definitely be treated to relieve symptoms regardless of no history of previous preterm birth or premature preterm rupture of the membranes.

Meta-analysis suggests that metronidazol in pregnant patients is not associated with increased teratogenic risk¹⁵. Nevertheless, lower doses of the drug are recommended to minimize exposure to the fetus.

The recommended regimen is metronidazol 250 mg orally three times a day for 7 days. Alternative regimens are metronidazol 2 g orally in single dose; clindamycin 300 mg orally twice a day for 7 days; metronidazol gel 0.75% one full applicator (5g) intravaginally twice a day for 5 days⁶.

Whether to treat pregnant women with asymptomatic BV is still controversial. In prospective study of cohorts of low risk pregnant women the finding of asymptomatic BV was not associated with increase preterm birth rate¹⁶. Several randomized prospective studies examined the effect of treatment for BV on adverse outcome of pregnancy^{14,17-24}. The treatment regimens were different in different studies. Starting times range from gestational age of 14 weeks to 24 weeks gestation. Doses of metronidazol were reduced to a maximum of 750 mg per day given up to 7 days¹⁸⁻²⁰ or in two doses of 2 g¹⁴, and in one study Erythromycin was added²⁰. Clindamycin when used was applied intravaginally 2% 5g 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 sample size was small and in some no distinction was made between symptomatic and asymptomatic patients. The population of pregnant woman was at low risk in some^{14,19,21,22,24} and with a history of preterm birth in others^{14,18,20,23,24}. The effects of the treatments differed, succeeding in reducing preterm deliveries in low risk populations in two studies^{22,24} but with no effect in the others^{14,19,21}. A benefit from the treatment was observed in three studies of high-risk populations¹⁸⁻²⁰ but no effect could be demonstrated in the rest^{14,21-24}. In the largest most recent randomized controlled study no effect could be found for metronidazol in either low or high-risk pregnant women¹⁴. The recommend approach in pregnancy is to treat the symptomatic patient and to screen the high-risk population, treating the high-risk women with asymptomatic BV¹⁷.

Probiotic Bacteria

In 1989 Probiotic was define 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 has been further refined in 1998 to “living microorganisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition”²⁷.

The Lactobacilli belong to the 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 dominant part of the vaginal microflora during birth and about 25 hours after birth the colonic microflora primarily consists of lactobacilli and bifidobacteria²⁸. Evidence has been collected proving that administration of selected microorganisms including non-pathogenic yeast and several genera of bacteria including lactobacilli and bifidobacteria is beneficial in the prevention and treatment of certain intestinal infection and possibly vaginal infection²⁹.

The concept that lactobacilli might be useful in displacing and replacing harmful microorganisms on mucosal surfaces dates back to Elie Metchnikoff in 1908³⁰.

Following anecdotal reports, Hilton in 1992³¹ was the first to perform a controlled crossover study to examine whether daily ingestion of yogurt containing lactobacilli acidophilus prevents vulvovaginal candidal infection. It was found that daily ingestion of 8 ounces of yogurt containing lactobacilli acidophilus decreased candidal colonization and infection. This study has been scrutinized because of several reasons. Previous in vitro studies examining the adherence of *Lactobacillus* species to normal human vaginal epithelial cells found that *Lactobacillus 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 lactobacilli³². Furthermore, the study lacked a control with pasteurized yogurt and finally, patients use *Lactobacillus*-containing preparations, often in preference to topical antifungal agents. Editorial comment of the study concluded that the true value of this approach deserves further analysis³³.

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 microorganisms³⁴. Nevertheless, only a very few studies examined the effect of probiotics in the treatment of BV. In a letter to *Lancet* in 1987, Fredricsson et al³⁵ presented clinical evidence suggesting that an intravaginal application of yogurt for the treatment of BV is rarely effective.

Neri et al³⁶ showed for the first time favorable results in treating a total of 32 women with BV in the first trimester of pregnancy with intravaginal applications of yogurt. The results indicated that the continuous correction of vaginal pH and *Lactobacillus* flora is crucial for normal vaginal ecology.

Shalev et al³⁷ treated women with at least 4 documented episodes of vaginal candidiasis or BV during one year. The patients were randomly assigned to one of

two groups. In the first group patients were instructed to eat 150 mL of yogurt that was enriched with *L. acidophilus* daily for 2 months; then for 2 months patients were not supposed to eat yogurt at all, and then for the next 2 months they switched to eating 150 mL of pasteurized yogurt daily. In the second group, patients began by eating the pasteurized yogurt diet; then, after 2 months without yogurt, they switched to eating the *Lactobacillus*-enriched yogurt.

A yogurt was chosen for the study that yielded more than 10 colony-forming units per milliliter of *L. acidophilus*, which is a hydrogen peroxide-producing strain.

Patients were seen at monthly intervals for at least 6 months. Seventy-five women who reported a history of recurrent candidal vaginitis, BV or both were recruited for the study but only forty-six women entered into the study. Twenty women had BV, 18 had candidal vaginitis and 8 had both vaginal conditions at the start of the study. Twenty-three randomly assigned patients began eating the yogurt that contained *Lactobacillus* (group 1), and the other 23 patients began eating the pasteurized yogurt (group 2).

Before entering the study, (24%) of the women had positive vaginal cultures for *L. acidophilus*; after 1 or 2 months of eating yogurt that contained *Lactobacillus*, there was a significant difference ($P < .05$) between the 2 groups. The same pattern was demonstrated in stool cultures for *L. acidophilus*. When *L. acidophilus* was present in the rectal culture, the probability of its presence in the vagina was 68%.

There was a steady reduction in vaginal cultures that were positive for *Candida* in both groups—from 60% in the first month to 20%–28% after 2 months of treatment .

A significant reduction in the episodes of BV was noted in group 1—from 60% of the episodes of BV at the start to 25% after 1 month compared with 50% of the episodes of BV in group 2 ($P = .004$). The significant difference continued after 2 months.

There was a significant reduction in the number of episodes of BV during the time when yogurt that contained *L. acidophilus* was eaten compared with that during the period when pasteurized yogurt was eaten ($P < .001$).

In the women who completed the original study protocol, there was a significant difference in the number of isolated positive vaginal cultures with *L. acidophilus*, with 12 (86%) of 14 visits during the period of eating yogurt that contained *L. acidophilus* compared with 5 (36%) of 14 visits during the period of eating pasteurized yogurt ($P = .001$).

Yogurt that contained *L acidophilus* was chosen for the study because evidence suggested that *L acidophilus* had improved survival on passage through the gastrointestinal tract compared with other *Lactobacillus* species³⁸.

The possibility of using lactobacilli is promising. Although it still needs scientific confirmation, probiotics can be especially important in pregnant women in reducing preterm birth rate. It has been claimed that intrauterine infection with BV may antedate the pregnancy³⁹. Probiotics can safely be used before pregnancy and in the first trimester, as well as an adjunctive to therapy in the second trimester, avoiding the potential side effects and teratogenicity of the standard treatments.

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