

The effect of treating bacterial vaginosis on preterm labor

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Objective: Multiple studies suggest that bacterial vaginosis (BV) causes preterm labor; yet its routine treatment remains controversial. In order to help to elucidate this controversy, we performed a thorough review of studies with levels of evidence ranging from I to II–II.

Methods: We searched for all of the studies from the years 1994 to 2001 via Medline's database, including MD Consult and Ovid Mednet.

Results: Several trials discovered a decrease in the incidence of preterm labor when BV was treated, but most of those trials were performed on women with a history of preterm labor. However, the majority of trials reviewed advise against treatment of a general low-risk obstetric population, as there was no significant decrease in preterm labor.

Conclusions: Therefore, based on the above studies and the current guidelines of the Centers for Disease Control and Prevention (CDC), treating pregnant women in high-risk populations who are diagnosed with BV provides the clinician with an opportunity to possibly prevent preterm labor in this population. In nulliparous women without a history of preterm birth, treatment is recommended if other risk factors are present (e.g. gonorrhea or chlamydia). However, in the general low-risk populations, routine screening is not indicated.

Key words: INFECTION; MOBILUNCUS; ANTIBIOTICS; VAGINITIS; PREMATUREITY

Premature births remain a serious problem in the USA, occurring in 11% of all pregnancies. Preterm birth, defined as delivery of an infant before 37 weeks' gestation, is also the leading cause of neonatal mortality and morbidity in the developed world. In the USA alone, an excess of \$4 billion¹, or 57% of direct nursery costs² can be attributed to the care of premature infants. In addition, infants who survive exhibit an increased risk of long-term morbidity, chronic lung disease, cerebral palsy, developmental delay, and visual and hearing impairment^{1,2}.

Causes of preterm labor vary, but infection is highly suspect. Up to 80% of early premature births are associated with an intrauterine infection prior to the rupture of membranes. Asymptomatic

bacteriuria, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and bacterial vaginosis (BV) have all been associated with an increased risk of preterm birth³. The exception is vaginal yeast infections⁴. Risk factors for preterm delivery are listed in Table 1. Multiple studies suggest that BV is a cause of preterm labor, yet its routine treatment remains controversial^{5–8}.

In conjunction with preterm delivery, BV in pregnant patients is associated with premature rupture of membranes, infection of the amnion and chorion, histologic chorioamnionitis and infection of amniotic fluid. Flynn *et al.*⁵ noted a 60% increase in the risk of preterm delivery in the presence of BV. Another study by Hillier *et al.*⁶ associated BV with risk of spontaneous preterm

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Table 1 Risk factors for preterm labor^{1,2}

History of preterm birth
Multiple gestation
Bacterial vaginosis
Urinary tract infection
Crack cocaine usage
Abruption
Second- and third-trimester vaginal bleeding
Maternal age under 16 years or over 40 years
African-American race
History of uterine surgery
Smoking
Strenuous work
Polyhydramnios and oligohydramnios
Cervical infections
Cervical incompetence
Pre-eclampsia
Premature preterm rupture of membranes
Domestic violence
Retained intrauterine device

birth by a factor of 1.5 to 3 in high-risk women, while other studies suggest that BV almost doubles the risk of spontaneous preterm delivery⁷.

Although BV is present in almost 20% of pregnant women, most cases remain asymptomatic, and not all women with the condition will deliver prematurely⁸. It is postulated that there exists a subgroup of high-risk women (e.g. those who have vaginal colonization with *Mycoplasma hominis*). African-American women may also exhibit 200–300% more BV than white populations^{7,8}. The exact conditions under which BV directly correlates with preterm labor are unknown⁵.

The purpose of this paper is to review the recent literature addressing the association between BV and preterm birth⁴.

METHODS

In order to perform this review, we searched the Medline database, including MD Consult and Ovid Mednet for the years 1994–2001. Some of the search terms included preterm labor, BV, treatment, metronidazole, clindamycin, and vaginitis.

RESULTS

Hauth *et al.* (Level I study in 1995) treated pregnant women with a history of preterm birth

or weight < 50 kg and a positive diagnosis of BV⁷. Treatment consisted of metronidazole (250 mg three times a day for 7 days) and erythromycin (333 mg three times a day for 14 days). The results of this 2:1 double-blind randomization trial revealed a decreased incidence of preterm delivery (< 37 weeks) for the entire study population (odds ratio, OR, 0.48; 95% confidence interval, CI 0.28–0.81), as well as for a subset of patients with a previous preterm delivery (OR, 0.48; 95% CI, 0.25–0.90). Women who were diagnosed with BV at the initial visit (24 weeks) and who received antibiotics rather than placebo presented with fewer preterm deliveries. Since this treatment benefit was only observed at initial examination, the overall results do not support mid-trimester treatment with metronidazole and erythromycin in women at risk for preterm delivery without BV. There are no data to suggest that treatment of low-risk pregnant women with BV decreases the rates of prematurity⁷.

Over a period of 3 years, Morales *et al.* (level I study in 1994) screened for BV in women between 13 and 20 weeks with a singleton gestation and a history of preterm birth via a double-blind randomized trial. The 80 women with a positive screen received either metronidazole (250 mg three times a day) or a placebo for 7 days. The study showed a significant decrease in delivery prior to 37 weeks among women taking metronidazole (18%) compared with those on placebo (39%) ($p < 0.05$). In the metronidazole group there were significantly fewer hospital admissions for preterm labor, cases of premature rupture of membranes, and low birth weights⁹.

In 1995, McGregor *et al.* (level I study) performed a prospective, controlled treatment trial of 1260 subjects to study the effect of clindamycin on pregnant women with BV. Women who were treated with 300 mg of clindamycin orally twice daily for 7 days showed a reduction in preterm birth (relative risk 0.5; 95% CI, 0.3–0.9), and the authors recommended that women at risk for preterm birth with BV should be screened and treated¹.

In 1997, McDonald *et al.*¹⁰ conducted a multicenter, randomized, placebo-controlled trial of 879 women at 19 weeks' gestation, but failed to demonstrate a reduced preterm birth rate

among pregnant women with BV or those with a heavy growth of *Gardnerella vaginalis* (level I). The intention-to-treat analysis showed no difference between the treatment and placebo groups in overall preterm birth (31/429 [7.2%] vs. 32/428 [7.5%]) or spontaneous preterm birth rate (20/429 [4.7%] vs. 24/428 [5.6%]). However, among women with a previous preterm birth, those treated with oral metronidazole (400 mg twice daily for 2 days at 24 weeks' gestation, and again at 29 weeks) demonstrated a marked reduction in spontaneous preterm birth rate (OR, 0.14; 95% CI, 0.01–0.84)¹⁰.

A meta-analysis from the Cochrane database determined that preterm birth rates did not differ significantly between treated and non-treated pregnant patients with BV (OR, 0.78; 95% CI, 0.60–1.02), yet a subgroup of women with a previous preterm birth demonstrated a significant decrease in the incidence of preterm birth, with an odds ratio of 0.37 (95% CI, 0.23–0.60)³. This meta-analysis of 1504 women from a total of five trials using amoxicillin, clindamycin and metronidazole did not recommend screening and treating all pregnant women for BV in order to prevent preterm birth.

Carey *et al.*¹¹ recently conducted a randomized, double-blind clinical trial of the use of metronidazole to treat asymptomatic BV. Treatment did not reduce the frequency of delivery before 37 weeks' gestation (relative risk in the metronidazole group, 1.0; 95% CI, 0.8–1.2). This clinical trial differed from previous attempts because it was larger (1953 subjects) and it studied the general obstetrical population, not just women with a history of preterm delivery. Treatment involved a shorter course of metronidazole therapy with two 2 g doses during a 48-hour period, and a second treatment of the women between 24 and 30 weeks' gestation. These researchers recommended the longer course of therapy to eradicate upper genital tract organisms¹¹.

The results of this study supported those of McDonald *et al.*¹⁰ in that metronidazole did not reduce preterm delivery among the general population of pregnant women, nor did it reduce hospital admissions for preterm labor or preterm premature rupture of the membranes, postpartum endometritis, clinical intra-amniotic infections,

vaginal infections serious enough to require treatment, and treatment with tocolytic drugs. The placebo and metronidazole groups did not differ with regard to incidence of admissions to the neonatal intensive-care unit, passage of meconium, or fetal death/neonatal death. This study found that routine screening of pregnant women for asymptomatic BV and treating the latter with a short course of orally administered metronidazole did not reduce the risk of preterm birth, despite its effectiveness in eradicating BV. Studies do not support the use of metronidazole treatment in pregnant women with asymptomatic BV who are considered to be at either high or low risk for preterm delivery¹¹. Studies by McDonald *et al.*¹⁰, Morales *et al.*⁹ and Hauth *et al.*⁷ did find evidence of a decreased incidence of recurrent preterm delivery among women with a prior preterm delivery treated with metronidazole or metronidazole/erythromycin.

The findings of Joesoef *et al.*¹² concur with those of Carey *et al.*¹¹. This multicenter, double-blind, randomized, placebo-controlled trial failed to demonstrate a reduction in preterm delivery (level I, 1995) in 745 women between 14 and 26 weeks' gestation who were diagnosed with BV (via Gram stain score > 6) with 2% clindamycin vaginal cream or with a placebo cream for 7 days. Although 15% of the women treated with clindamycin had a preterm delivery, only 13.5% of placebo patients did (OR, 1.1; 95% CI, 0.7–1.7). The authors proposed that the increased frequency of preterm delivery might be caused by a transient increase in vaginal colonization by *Escherichia coli* and *Enterococcus* 1 month after therapy. Since *E. coli* is linked to an increased risk of preterm delivery, this may explain the value of 15%, compared with the 13.5% difference found in the study by Joesoef *et al.*¹².

In 1994, McGregor *et al.*¹³ evaluated 271 women between 16 and 27 weeks' gestation in a double-blind trial (level I). Women who were diagnosed with BV were treated with 2% clindamycin vaginal cream or placebo for 7 days. Although 2% clindamycin vaginal cream was effective in treating BV during pregnancy ($p = 0.001$) it was not permanent, as the condition gradually returned, and treatment did not reduce the risk of prematurity during the second trimester.

Possible reasons cited include the inadequate power of the study, the timing of treatment, and the use of local vaginal treatment¹³.

In 2001, Kekki *et al.*¹⁴ performed a multicenter, randomized, double-blind, placebo-controlled trial (level I) which showed that the treatment of BV in early pregnancy with vaginal clindamycin for 7 days did not decrease the rate of preterm deliveries or peripartum infections. In 375 randomized subjects, preterm delivery occurred in 5% of the clindamycin group and 4% of the placebo group (OR, 1.3; 95% CI, 0.5–3.5). The efficacy of intravaginal clindamycin can be as high as 90% in studies on non-pregnant women, and is similar to that of oral metronidazole. The subjects included a low-risk population of healthy women with singleton pregnancies and without a history of preterm delivery¹⁴. The results are similar to the conclusion of McGregor *et al.*¹³ that topical treatment in early pregnancy reduced vaginal fluid mucinase and sialidase, but failed to reduce the rate of preterm births¹⁴.

A recent randomized controlled trial by Kurkinen-Raty *et al.*¹⁵ assessed the efficacy of vaginal clindamycin in reducing preterm birth (level I). Of the 1956 women without a history of preterm delivery who were screened at the first antenatal visit (gestational week 12), 143 women tested positive for BV. After randomization and treatment with clindamycin or placebo, the preterm birth rate in the clindamycin group was 13.7%, compared with 6.0% in the placebo group (OR, 2.5; 95% CI, 0.6–10). This study therefore supports the evidence that vaginal clindamycin treatment of BV in the first trimester does not reduce the risk of preterm birth¹⁵.

In 1999, French *et al.*¹⁶ evaluated the association between BV, first-trimester vaginal bleeding and preterm labor in 1100 pregnant women who were enrolled in a prospective observational study (level II–II). It was determined that treatment of BV with clindamycin (300 mg orally twice daily for 7 days) significantly reduced the risks of preterm birth among women without first-trimester bleeding (relative risk, 0.37; 95% CI, 0.16–0.88). Although the overall population of women with both BV and first-trimester vaginal bleeding experienced reductions in preterm birth, the finding was not

statistically significant (relative risk, 0.52; 95% CI, 0.18–1.55)¹⁶.

Several authors have proposed that the timing of the diagnosis and/or treatment is important if preterm labor is to be decreased. A level II–II study by Meis *et al.*¹⁷ highlighted the effect of timing of diagnosis on BV and the incidence of preterm labor. Women who tested negative at 24 weeks but were positive when tested again at 28 weeks had the highest likelihood of preterm birth (OR, 2.53; 95% CI, 1.32–4.85; $p = 0.005$)¹⁷.

Riduan *et al.*¹⁸ found the opposite to be true (level II–I trial). Women who tested positive for BV at 24 weeks and received antibiotics showed a significantly decreased incidence of preterm birth (OR, 0.44; 95% CI, 0.11–1.91). The authors found that the presence of BV at 16 weeks was more predictive of preterm delivery than its presence at 28 to 32 weeks¹⁸.

Table 2 provides a concise summary of the articles reviewed above.

DISCUSSION

Preterm labor may be classified as either physiologic or pathologic. Physiologic preterm labor describes a normal initiating factor that occurs too early in pregnancy, while pathologic preterm labor results from an abnormal initiating factor with timing being a distinguishing factor. The earlier in pregnancy preterm labor occurs, the more likely it is that a pathologic etiology exists. Prior to 16 weeks' gestation, BV is related to preterm delivery by a risk factor of 5 to 7.5. After 26 weeks' gestation, the risk factor drops to 1.4 to 1.9^{19,20}.

BV, an overgrowth of anaerobic species that produce protease, phospholipase A2 and collagenases in the vagina²¹, is found in 800 000 pregnant women each year¹¹. There is disruption of the vaginal ecosystem that results in increased levels of anaerobes. BV alters the vaginal flora by decreasing the number of hydrogen-peroxide-producing *Lactobacillus acidophilus* organisms. Consequently, the levels of *G. vaginalis*, *M. hominis*, and *Mobiluncus* species increase rather than remaining in their normal state of suppression. The metabolic by-products of these

Table 2 Studies that have evaluated the effect of treatment of bacterial vaginosis on the incidence of preterm labor

Author	Year	Study type	Effect on preterm labor	Drug	Level of evidence
Hauth et al. ⁷	1995	Double-blind	Decreased in high-risk	Metronidazole/ erythromycin	Level I
Morales et al. ⁹	1994	Placebo controlled	Decreased in high-risk	Metronidazole	Level I
McGregor et al. ¹	1995	Prospective controlled treatment trial	Decreased in women at high risk	Clindamycin	Level I
McDonald et al. ¹⁰	1997	Randomized, placebo, controlled	Decreased only in subset with a history of preterm labor	Metronidazole	Level I
Cochrane database ³	1991 to 2001	Meta-analysis of controlled trials	No decrease in general population, but a decrease in those at high risk	Amoxicillin, metronidazole and/or clindamycin	Level I
Joesoef et al. ¹²	1995	Double-blind, randomized, placebo	No decrease in low-risk population	Metronidazole	Level I
Carey et al. ¹¹	2000	Randomized, double-blind	Asymptomatic general population without decrease	Metronidazole (short course)	Level I
McGregor et al. ¹³	1994	Randomized, double-blind	No decrease in women at 16 to 27 weeks' gestation	Clindamycin	Level I
Kekki et al. ¹⁴	2001	Double-blind, placebo	No decrease in low-risk population	Clindamycin	Level I
Kurkinen-Raty et al. ¹⁵	2000	Randomized, controlled	No significant decrease in low-risk population	Clindamycin	Level I
French et al. ¹⁶	1999	Prospective, observational	Decreased in low-risk population, but not statistically significant	Clindamycin	Level II-II

organisms include amines, which increase the vaginal pH, and exfoliation of vaginal epithelial cells results²².

Although the exact mechanism is not known, studies have shown that BV can cause infection of the upper genital tract, which acts as a premature birth trigger⁶. BV and *T. vaginalis* are also associated with many microorganisms that produce phospholipase A2 and C or phospholipase-like activity, and affected patients show increased levels of sialidase, phospholipase A2, prostaglandin E2 and interleukin-1(beta). The rise in levels of these enzymes may result in the decidual or fetal membrane cell fatty acid tissue stores releasing arachidonic acid², a precursor of the uterotonic prostaglandins.

Other explanations of an association between BV and preterm labor include activation of fetal and/or maternal inflammatory responses or proteolytic enzymes. Elevated vaginal or cervical levels of endotoxin, mucinase, sialidase and

interleukin-1(alpha) are found in women with BV, which suggests that the microorganisms produce cytokines⁶. These cytokines and the release of interleukin-1(beta) and tumor necrosis factor induce cyclooxygenase II, an enzyme that produces prostaglandins involved in parturition. Proteolytic enzymes that may overcome maternal mucous membrane defenses and impair fetal membrane strength and elasticity include collagenases, immunoglobulin A proteases, elastases, mucinases and/or sialidases².

Several studies have concluded that screening and treating for BV is futile, and one of the largest clinical trials to date found no difference in the treated low-risk pregnant population compared with the placebo¹¹. However, since the clinical diagnosis of BV need not be symptomatic, screening all pregnant women who have risk factors may be unnecessary and not cost-effective²¹, while the most advantageous time to screen and the optimum dosage of antibiotic is uncertain.

Although the *The Cochrane Library's* review is an excellent resource, our paper differs in that we have investigated different aspects of this approach. We have included not only level I but also level II studies. Furthermore, we included two studies that investigated the effects of timing on the treatment of BV^{17,18}. However, ultimately our conclusion is similar to that of the Cochrane review³.

To the clinicians who decide to screen for and treat BV, the most effective antibiotic appears to be oral metronidazole, which can be safely administered during pregnancy. Vaginal

clindamycin therapy has shown slight but statistically non-significant increases in preterm birth rate for the reasons discussed previously²³.

Analysis of the reviewed studies supports the current guidelines of the Center for Disease Control. Treating pregnant women in high-risk populations who have been diagnosed with BV can prevent preterm labor in these individuals. In nulliparous women without a history of preterm birth, the recommendation is to treat if other risk factors, such as gonorrhea or chlamydia, are present.

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