Effects of Metronidazole Therapy on Preterm Labor in Women with Bacterial Vaginosis

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Abstract- Regarding to prevalence of preterm labor and its consequences, there are different reports on relationship between bacterial vaginosis and preterm labor. This study was performed to evaluate the effect of metronidazole therapy on preterm labor in women with bacterial vaginosis. This randomized clinical trial was performed on 120 women suffering from bacterial vaginosis at 20-34 weeks of pregnancy, to evaluate the therapeutic effect of metronidazole to delay preterm labor in Shabih Khani maternity hospital in Kashan, Iran in 2002. Bacterial vaginosis was diagnosed based on clinical and laboratory findings. The patients were randomly divided into two groups. The patients in the case group received 500 mg metronidazole BID for 7 consecutive days, but the control group did not receive it. The demographic characteristics of the patients such as, pregnancy age, educational level and job of the spouse were similar at both case and control groups. Double-blind follow up of the patients at the whole stages of parturition and after delivery with respect to the delivery method, infection, and fever was done by other practitioner besides the main researcher. The results were analyzed statistically by chi-square, and Fischer's exact tests. 420 patients entered the study, of whom 120 (28.6%) had bacterial vaginosis. The antibiotic and control groups were not significantly different for maternal age, job of the spouse, and education. No difference was observed in spontaneous preterm birth before 37 weeks of gestation in antibiotic-treated compared with control group. Treatment with metronidazole in symptomatic women with a bacterial vaginosis in the late second trimester does not decrease the incidence of preterm delivery.

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Key words: Bacterial vaginosis, preterm labor, metronidazole

Introduction

Bacterial vaginosis (BV) is the most common cause of vaginitis in women of child bearing age, with prevalence of 5-60% across the globe (1, 2). The rate of occurrence depends upon the population studied: 17-19% in family-planning or student health clinics; 24-37% in sexually transmitted disease clinics; and 10-35% among pregnant women in the United States (3). BV is not outcome of a single organism. It represents a complex change in vaginal flora characterized by a reduction in the prevalence and concentration of hydrogen peroxide-producing lactobacilli and an increase in the prevalence and concentration of the *Gardnerella vaginalis*, Mobiluncus species, *Mycoplasma hominis*, anaerobic gram-negative rods belonging to the genera Prevotella, Porphyromonas, *Atopobium vaginae* and Bacteroides; and Peptostreptococcus species(4). Approximately 50-75% of women with BV are asymptomatic (5, 6). Those with symptoms present with an unpleasant "fishy smelling" discharge that is more noticeable after unprotected intercourse (7). Pregnant women with BV appear to be at higher risk of preterm delivery (3, 8). The diagnosis of BV is clinical based on criteria that are simple and useful in office practice (9). BV resolves spontaneously in up to one-third of non-pregnant and pregnant women (10, 11). Treatment is indicated in women with symptomatic infection and those with asymptomatic infection prior to abortion or hysterectomy; asymptomatic pregnant women with previous preterm births may also benefit, but screening and treatment of these women is controversial. Metronidazole or clindamycin administered either orally or intra-vaginally will result in a high rate of clinical cure with 70-80% at four weeks of follow-up (12). Treatment is appropriate for pregnant women with symptomatic bacterial vaginosis (13).

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Table 1. Socio-demographic characteristics of the women referred to Shabih-Khani maternity hospital

	Control group	Treatment group
No. of pregnancies	60	60
Maternal age (year)		
Mean (SD)	27.6 ± 5.6	25.7 ± 6.4
Height (centimeter)		
Mean (SD)	159 ± 0.1	160 ± 0.3
Weight (kilogram)		
Mean (SD)	72 ± 0.4	73 ± 0.1
Measures of social status		
Good	32(53.3)	30(50)
Intermediate	11(18.3)	8(13.2)
Weak	17(28.3)	22(36.7)
Educational qualifications		
Uneducated	29(48.3)	26(43.3)
High school	31(51.7)	34(56.7)

Screening and treatment of asymptomatic BV is controversial. Most studies have reported an increased risk of preterm birth in these women; the pooled odds ratios for prematurity from two meta-analyses were 1.8 and 2.2 (14).

Despite the association between BV and preterm birth, most studies in general obstetric populations have not found that treatment of asymptomatic infection reduced the incidence of preterm labor or delivery (15-17). A Cochrane review of ten trials involving 4249 pregnant women reported that antibiotic therapy was highly effective in eradicating infection, but did not significantly reduce the odds of preterm birth at < 37 weeks (OR 0.95, 95% CI 0.82-1.01), < 34 weeks (OR 1.20, 95% CI 0.69-2.07), or < 32 weeks (OR 1.08, 95% CI 0.70-1.68) (15). Other systematic reviews have come to similar conclusions (18-20). Based upon these data, screening and treating all pregnant women with asymptomatic BV to prevent preterm birth and its consequences is not recommended. However, when the Cochrane reviewers separately analyzed the subgroup of women with a history of one or more prior preterm births, they found that detection and treatment of asymptomatic BV in this population appeared to markedly reduce the rate of preterm pre-labor rupture of membranes (OR 0.14, 95% CI 0.05-0.38) and low birth weight (LBW) (OR 0.31, 95% CI 0.13-0.75), but did not significantly affect the risk of subsequent preterm birth (OR 0.83, 95% CI 0.59-1.17) (15). The objective of our study was screening of BV and treat symptomatic women with metronidazole and observation of the effect on delivery prior to 37 completed weeks (primary outcome).

Patients and Methods

The study was conducted in the Shabih-Khani maternity hospital in Kashan, Iran. The randomized consent design of clinical trial was approved by the Ethics Committee in Kashan University of Medical Sciences with the modification that all women were informed about the study procedure during the initial visit to Shabih-Khani maternity hospital. Participants recruited were between 20 and 34 weeks of gestational age at their initial visit to the clinic.

If the woman agreed to participate in the study, a specimen of vaginal fluid was collected by the physician or the midwife from the posterior or the lateral vaginal wall and placed on a microscopic slide. The slides were air dried and observed at the department of microbiology, using Gram staining. BV was confirmed with homogeneous, grayish-white discharge, gram staining of vaginal secretions, Vaginal pH greater than 4.5, Clue cells on saline wet mount, and Positive whiff-amine test, defined as the presence of a fishy odor when KOH (10%) is added to vaginal discharge samples. Enrolment of participants to the study began in March 2002 and continued until October 2002. During this period, approximately 420 women were registered in the Shabih-Khani clinic, 120 had bacterial vaginosis and all of these 120 consented to participate in the study. All women with BV were randomized to either an intervention group with a 7-day regimen of treatment with metronidazole (500 mg orally BID) or a control group to remain untreated and uninformed of their BV status as stipulated in the pre-randomized consent design for clinical trials.

Only women who were diagnosed with BV and randomized to the intervention group were told the result of their vaginal smear. Metronidazole treatment usually started within a week of diagnosis. Clinicians caring for the BV-positive group randomized to non-treatment were not told of the diagnosis. In the Kashan, where this study was conducted, all pregnant women attended to the Shabih-Khani maternity hospital which belongs to the public healthcare system. There is no private clinic care alternative. Therefore, all women studied had similar healthcare management throughout pregnancy. Pregnancy data were collected through the Medical Birth Register. Survival analysis was done with chi-square test and Fischer's exact tests. The level of statistical significance was set to $P < 0.05$.

Results

A total of 420 women were screened for BV. 120 (28.6%) women had BV, 60 women were classified as treated and 60 as non-treated. Socio-demographic characteristics of studied women are shown in Table 1. The mean age of the women in the intervention group was 25.7 ± 6.4 years (mean ± SD), and the mean age of the women in the control group was 27.6 ± 5.6 years (mean ± SD).

There were 4 cases of delivery prior to 37 completed gestational weeks, 2 (3.3%) in the intervention group and 2 (3.3%) in the control group. No statistical difference was observed in spontaneous preterm birth before 37 weeks gestation in antibiotic treated compared with control group.

Discussion

This study did not show any significant reduction in the incidence of preterm birth prior to 37 completed weeks associated with the treatment of BV with administration of metronidazole. Treatment of BV among women at high risk for preterm birth decreases the risk for preterm delivery (21-22). However, treatment of BV among women at moderate or low risk has no major effect on the risk for preterm birth or prepartum infections (16-17, 23-24).

On the basis of this study and others in the literature, it seems that metronidazole alone has no benefit in the prevention of preterm delivery in high risk women. We therefore do not recommend continued use of metronidazole in the clinical setting for the prevention of preterm delivery.

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