Treating asymptomatic bacterial vaginosis in pregnancy

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Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med* **2000;342:534-40.**

Research question

Vaginal swabs done at routine antenatal visits frequently come back positive for *Gardnerella vaginalis*, but most of the women have no symptoms of bacterial vaginosis (BV). Is there any benefit to treating these women?

Type of article and design

Prospective, randomized, double-blind, placebo-controlled study.

Relevance to family physicians

Bacterial vaginosis represents a change in the complex balance of microflora in the vagina. Infection occurs when there is a relative decrease in lactobacilli (normally 95% of the total floral population[1]) and a corresponding increase in *G vaginalis*, *Mycoplasma hominis*, and Gram-negative anaerobes.

Clinically, the symptoms of BV include a fishy odour (sometimes more pronounced after sexual intercourse), vaginal itch, dyspareunia, and dysuria. Discharge is typically homogeneous, white or grey, and adherent to the walls of the vagina. The name "vaginosis" indicates an absence of underlying vaginal erythema or edema.[2]

Some researchers have suggested that BV during pregnancy precipitates preterm labour. It is thought that bacterial by-products, such as phospholipases, could trigger prostaglandin production and stimulate contractions, while protease by-products would weaken the collagen structure in the gestational sac and allow premature rupture of membranes.[3] The studies supporting this theory were plagued with methodologic flaws and included only high-risk patients already predisposed to preterm labour.

Bacterial vaginosis is the most common vaginal infection in women of reproductive age with a yearly incidence of 15% and a prevalence of 9% to 23%.[4] During pregnancy, BV has a prevalence of between 10% and 30%.[4]

Preterm deliveries account for 70% of all perinatal mortality and 50% of all long-term neurologic morbidity. The most serious sequelae occur in infants born at <32 weeks' gestation or weighing <1500 g.[3] Overall, approximately 10% of all deliveries are preterm (<37 weeks).[3]

Overview of study and outcomes

The goal of this study was to determine whether screening asymptomatic pregnant women for BV and treating those with positive criteria for BV would decrease the risk of preterm delivery. The study was funded and carried out by a national health organization in the United States. Data were collected from community-based hospitals.

Primary outcomes included preterm delivery (<37 weeks, <35 weeks, <32 weeks) and low birth weight (<2500 g, <1500 g). Secondary outcomes were rates of these events in high-risk women (previous preterm delivery of any cause, race, prepregnancy weight <50 kg) and antenatal complications in mother or child.

Initially, 29 625 women between 8 and 23 weeks' gestation were assessed for risk of preterm labour. Women were excluded if they had had previous fetal deaths, fetuses with life-threatening anomalies, multiple gestations, or cervical cerclage; were concurrently taking antibiotics or other drug therapy; had contraindications to metronidazole use; or were unavailable for follow up. Women with previous preterm deliveries were included in the study. Women were included in the study only if they were asymptomatic, which was defined as presenting for

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routine prenatal care with no vaginal symptoms (ie, odour, discharge, itch).

A total of 21 965 women met the initial study criteria and had vaginal swabs taken. The swabs were used to determine vaginal pH, to provide culture for bacterial growth, and to determine the Gram stain score (developed and validated by Nugent et al[5]). Women were identified as BV-positive if they had a Gram stain score of ≥7 and a vaginal pH of >4.4.

The 6540 women identified as BV-positive on vaginal swab screening were subjected to further inclusion or exclusion criteria. Only women between 16 and 24 weeks' gestation were included. Women were excluded if they had a vaginal pH of <4.4; could not arrange for follow up; had used antibiotics since the initial screening; had been screened more than 8 weeks previously; had evidence of infection with trichomoniasis, syphilis, gonorrhea, or chlamydia; or met any of the initial exclusion criteria.

At the time of randomization, women were examined by ultrasound for gestational age if they had not already had that examination. A second swab was taken for pH, Gram staining, and *T vaginalis* cultures. Results of these tests were concealed. Subjects remaining in the study were then randomized to either treatment with 2 g of metronidazole by mouth (n = 966) or to placebo (n = 987). At 24 to 30 weeks, vaginal swabs were taken again and a second course of the same treatment was undertaken.

Results

Most subjects (98.3%) were followed up after delivery. There were no significant differences between the two groups in primary outcomes (prematurity and low birth weight). All 95% confidence intervals (CI) crossed 1.0. With respect to secondary outcomes, there were no significant differences for any of the proposed risk factors (previous preterm delivery, gestational age at randomization, race, low prepregnancy weight, or trichomoniasis co-infection at randomization).

Adverse effects were significantly more frequent in the treatment group (21.9% versus 9.1%, *P*.10). Gastrointestinal symptoms affected 19.7% of women in the treatment group but only 7.5% in the placebo group. Complaints of vomiting were the most frequent: 9.7% in the treatment group and 2.8% in the placebo group.

Analysis of methodology

This randomized, double-blind, placebo-controlled study had strict exclusion and inclusion criteria. Intention-to-treat analysis was carried out, and follow up was excellent. Treatment and placebo groups were similar in their characteristics.

Because the study population is similar to that in most of our communities and the patients similar to those family physicians see, this paper can inform us in triaging and treating our pregnant patients appropriately. The treatment protocol used in the study is similar to that used routinely by family physicians, which furthers its applicability.

Application to clinical practice

According to this well designed prospective study, treating pregnant women with clinically asymptomatic BV does not reduce rates of preterm delivery or decrease numbers of low-birth-weight babies. Results of subgroup analysis also suggest there is no benefit in treating high-risk pregnant women with asymptomatic BV. Although common practice would be to treat these high-risk women, this practice is not supported by results reported in this paper.

Currently, BV is identified through vaginal swabs that, surprisingly, are only 50% specific! In 1983, Amsel and colleagues[6] provided clinicians with criteria for making an objective diagnosis of BV (three of the following four criteria had to be met: homogeneous white or gray discharge that adheres to vaginal walls, pH >4.5, clue cells in >20% of a wet mount, and positive results from a potassium hydroxide whiff test). Kits for rapid diagnosis (similar to a urine dip stick) that incorporate the Amsel criteria will be available soon. This testing method will be more sensitive and specific for screening appropriate patients for BV.

If patients have symptoms, they should of course be treated appropriately according to the 1997 Society of Obstetricians and Gynecologists of Canada's guideline on BV.[2] Current medical treatments include metronidazole (500 mg twice daily for 7 days or 2 g in a single dose) and clindamycin (300 mg twice daily for 7 days).[7] Topical preparations have similar efficacy but are more likely to cause vaginal candidiasis. A meta-analysis recently found no increased risk of teratogenicity in fetuses exposed to metronidazole during the first trimester.[8,9] Routine screening and treatment of male partners is not indicated.

Bottom line

- Regardless of their risk level, this paper does not support treating asymptomatic women with positive cultures for *G vaginalis*. Treatment does not prevent preterm delivery or low-birth-weight infants.
- When assessing pregnant women with vaginal discharge, physicians should consider using stringent diagnostic criteria, such as the Amsel criteria, for diagnosing BV.

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Points saillants

- Quel que soit leur degré de risque, le présent article ne préconise pas le traitement des femmes asymptomatiques dont les résultats de cultures indiquent positivement la présence de *G vaginalis*. Le traitement ne prévient pas l'accouchement prématuré ni le faible poids chez le nouveau-né.
- Lorsqu'ils procèdent à l'évaluation de femmes enceintes présentant des écoulements vaginaux, les médecins devraient envisager le recours à des critères diagnostiques stricts, comme les critères Amsel, pour le diagnostic de la vaginose bactérienne.

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