Obstetrica şi Ginecologia LXV (2017) 199- 204 **Review article**

BACTERIAL VAGINOSIS IN PREGNANCY: professional diagnostics as a basis for an optimized therapy

Octavia Cionca, Z. Hadnagy, A. Murariu, Mihaela Zahner

Collective for Research in Obstetrics – Gynecology and Neonatology, Emergency Municipal Clinical Hospital Timisoara, Romania

Abstract

Bacterial vaginosis (BV) increases the risk of preterm birth and has been linked to a growing list of obstetric and gynecologic infections, and acquisition or transmission of human immunodeficiency virus and sexually transmitted infections. Adequate screening and treatment of pregnant women for BV will prevent the high risk of untreated infection affecting the fetus.

In generally gram stain-based diagnosis correlates well with clnical diagnosis and is an accepted diagnostic method.

Antibiotic therapy can significantly reduce the risk of preterm delivery

Rezumat: VAGINOZA BACTERIANĂ în SARCINĂ: diagnostic profesionist ca bază pentru o terapie optimizată

Vaginoza bacteriană creşte riscul naşterii premature, fiind asociată cu diferite complicaţii ale sarcinii şi cu dobândirea sau transmiterea virusului imunodeficienţei umane şi a infecţiilor cu transmitere sexuală. Screeningul adecvat şi tratamentul femeilor însărcinate pentru vaginoza bacteriană vor preveni riscul crescut de infecţie netratată care afectează fătul.

În general, interpretarea frotiului colorat Gram se corelează bine cu diagnosticul clinic şi este o metodă de diagnostic acceptată.

Tratamentul cu antibiotice poate reduce semnificativ riscul de naştere prematură

Cuvinte cheie: microbiom vaginal, antibiotice, naştere prematură

Introduction

Bacterial vaginosis (BV) is a clinical syndrome characterized by disequilibrium in the vaginal microbiota with decline in the number of lactobacilli.BV has also been linked to various pregnancy complications, including preterm labor and delivery, preterm premature rupture of membranes (PPROM), chorioamnionitis, postpartum endometritis, and abnormal Pap smears (1,2). Several studies demonstrate a higher prevalence of BV in the infertile population but do not confirm negative effects on pregnancy outcomes (3).

This review focus on disruptions in vaginal microbiome and link to pregnancy complications, screen and treat bacterial vaginosis.

BV-associated bacteria and pathophysiological mechanisms

It has been well established that the major source of intra-uterine colonization is vertical ascension from the vagina, and this is largely believed to occur during the second trimester, although the

CORESPONDENCE: Octvia Cionca, e-mail: avia36ro@yahoo.com
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actual timing is unknown and it is likely that this will vary between individual pregnancies (4).The colonization of microbes and/or inflammation of the chorio-decidual interface can induce the production of a cascade of cytokines that result in an inflammatory response. Bacteria also can have a more direct role in the pathogenesis of PTB by producing enzymes that degrade fetal membranes, or by inducing the synthesis and release of uterotonins such as prostaglandins, able to stimulate uterine contractions and cause preterm labor (5).

An association between endometritis and BV-associated anaerobic Gram-positive cocci has been established, confirming their role in reproductive morbidity.Also associated with BV infection in HIV-positive women are M. hominis and a combination of Bacteroides, Prevotella, Leptotrichia, Atopobium and Gardnerella known to attract CD4 cells to the mucosa, with a concomitant reduction in lactobacilli (6).

However, the pathophysiological mechanism through which BV affects the ongoing pregnancy remains unclear. To date, BV has only been considered as a trigger for an adverse inflammatory response during pregnancy (7).

Clinical characteristics of bacterial vaginosis (BV) and Laboratory Assessment

There is currently no consensus as to whether to screen for or treat bacterial vaginosis in the general pregnant population in order to prevent adverse outcomes, such as preterm birth (8).

In 1990 Helen McDonald warned that women with the risk of preterm labor had two types of abnormal vaginal secretion, first is BV and second are other aerobic microorganisms such as E.coli and Klebsiella (9).

There are two clinical diagnostics for BV. The Amsel criteria (Any-Symptom approach) searches for the presence of at least three of the following criteria: the presence of discharge, a positive whiff test, the presence of clue cells, and a pH greater than 4.5 (10).Vaginal pH determination is relatively sensitive, but less specific in detecting women with BV. Inclusion of whiff test along with pH test reduced the sensitivity, but improved specificity (11).

Despite the fact that the Amsel criteria do not require intensive training, it is not the most appropriate method to diagnose BV, due to its low specificity (12).

In research and laboratory settings, the Nugent score (N-Score approach),is a standardized 0–10-point scoring system based on the presence of three bacterial morphotypes: large gram-positive rods (*Lactobacillus* spp.), small gram-negative or gram-variable coccobacilli (*Gardnerella* and anaerobic spp.), and curved gram-variable rods (*Mobiluncus* spp.). A Nugent score (NS) of 0–3 is classified as the presence of "normal" flora, 4–6 as the presence of "intermediate" flora(mixed morphotypes), and 7–10 as BV(absence of lactobacilli and predominance of the other 2 morphotypes) (7,10,13).Carter et al results show that the classifiers associated with the 'Treat Any Symptom' version have better performances that the classifier associated with the 'Treat Based on N-Score Value' (10).

A weakness of diagnostic tests based on Gram-stained smears is the subjective nature of assessing bacterial cell morphology (14).Ravel *et al.* reported a strong correlation between high pH and high Nugent scores and the highest pH values were associated with community states not dominated by species of Lactobacillus (15).

Lactobacillus crispatus was negatively associated with all four clinical criteria and women with high levels of *L. crispatus* had low vaginal pH(16).L. crispatus dominance is protective against preterm birth, whereas L. iners dominance of the vaginal microbiota at 16 weeks of gestation is a risk factor for preterm birth (17).Different bacterial species have different associations with the four clinical criteria, which may account for discrepancies often observed between Amsel and Nugent (Gram stain) diagnostic criteria (16).

The commonest target for molecular identification of bacteria is the small ribosomal subunit of the 16S rRNA gene. Once the 16S rRNA gene has been sequenced, the variable regions can be used for species specific PCR in a qualitative or quantitative manner (18).

To improve BV diagnosis, several new molecular methodologies have been proposed,

fluorescence in situ hybridization (FISH) technology combines the simplicity of microscopic observation and the specificity of DNA/rRNA hybridization, allowing the detection of selected bacterial species and morphologic visualization (12).

Despite their limitations, cultivation studies remain an important part of vaginal microbiology and will need to be used in combination with cultivation-independent techniques (18).

Treatment of BV in pregnant women

The goal of the identification and treatment of these women would be to prevent the adverse outcomes of pregnancy or to prevent subsequent endometritis. As a general precaution, screening and treatment, if they are to be done, should be conducted at the earliest part of the second trimester of pregnancy after organogenesis is complete. In addition, lower doses of medication are preferable for pregnant women, to minimize exposure to the fetus (**Figure 1)** (19).

Data showed that antibiotic prophylaxis reduces the risk of preterm delivery in pregnant women with a previous preterm birth who had BV during the current pregnancy (20).Asymptomatic pregnant high-risk women (women with a prior preterm birth) may benefit from evaluation for BV and subsequent treatment (19).

Metronidazole, a nitroimidazole derivative, is a recommended treatment during pregnancy for bacterial vaginosis (BV).. Its efficacy for the treatment of symptomatic bacterial vaginosis ranges between 80% and 90% (21).Different doses were

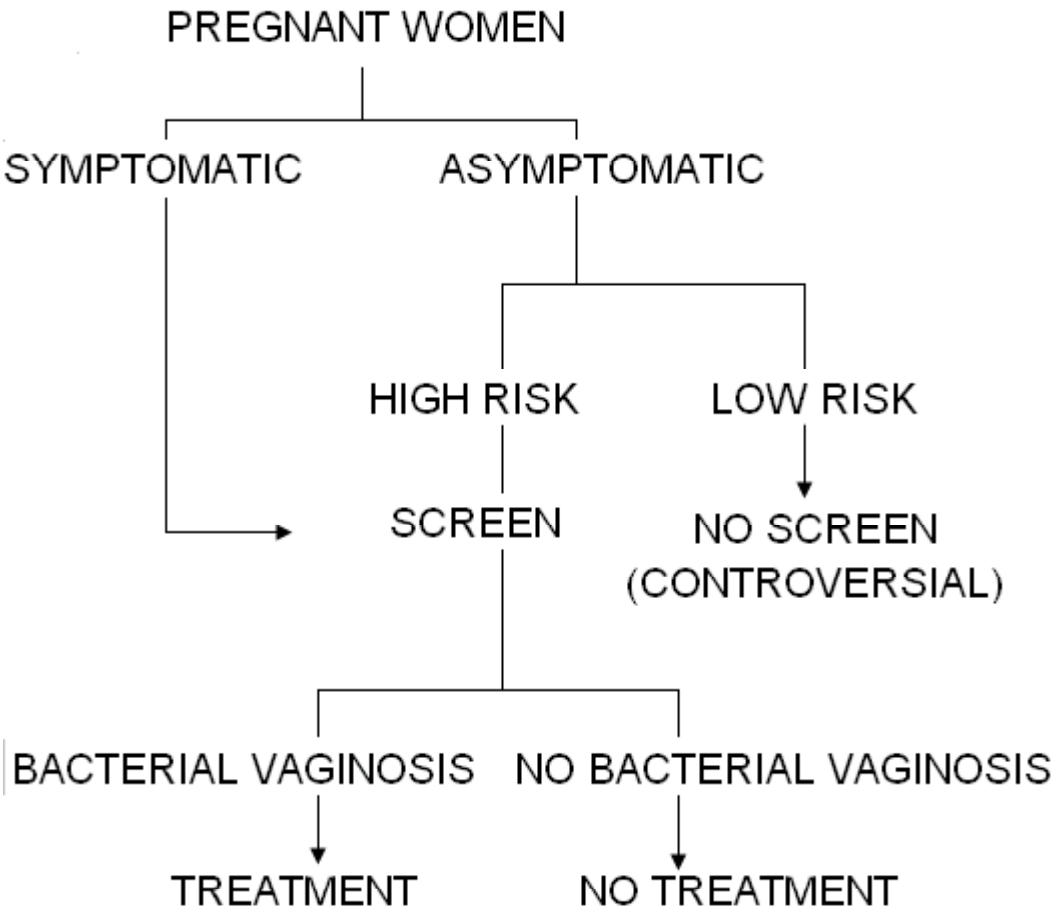

Figure1. A paradigm for treatment of bacterial vaginosis in pregnant women (19)

used at first treatment: women were prescribed 500 mg twice daily for 7 days, 250 mg three times daily for 7 days (22).

Clindamycin, at a dosage of 300 mg twice daily for 7 days (19, 23), is active against most organisms associated with BV, including G.vaginalis and Mobiluncus species (19). Mycoplasma hominis is resistent to metronidazole (24).

Regarding the route of antibiotic administration, vaginal antibiotic prophylaxis during pregnancy did not prevent infectious pregnancy outcomes (20).

In humans, metronidazole crosses the placenta. Therefore, there is a theoretical risk to the fetus that prenatal care providers may consider when making therapeutic choices for pregnant women (22).

Oral tinidazole has been studied as an alternative to metronidazole in trials in Europe and the United States. The evidence to date reveals similar cure rates with the possibility of a reduction in the number of doses required and in gastrointestinal side effects with tinidazole (23).

Inappropriate antibiotics used in inappropriate women at inappropriately late gestations do not reduce preterm birth. Conversely, a focused systematic review/meta-analysis demonstrated that the use of clindamycin early in pregnancy (< 22 completed weeks of gestation) before irreversible inflammatory damage occurs, in women with objective evidence of abnormal genital tract flora, demonstrated that clindamycin produced a significant decrease in late miscarriage and preterm birth (25,26).

More than 50% of women will experience recurrence of bacterial vaginosis within 6 months. It is not known whether this represents relapse or re-infection (27).Metronidazole appears to allow persistence of vaginal microbiome microorganisms which translate into frequent relapses (28).

Metronidazole or clindamycin play a significant role in the expansion of drug resistance in G. vaginalis and Prevotella, Bacteroides, and Peptostreptococcus spp (29). Future research should include follow-up of the BVand optimal treatment of this condition. Before embarking on multiple courses of therapy, it is recommended to reconfirm the diagnosis (23).

Most of the evidence suggests that treatment of bacterial vaginosis with antimicrobial agents (metronidazole or clindamycin) during pregnancy does not reduce the rate of preterm delivery, and this has been attributed to an inadequate characterization of the changes in the microbial ecosystem of the lower genital tract in patients who subsequently delivered preterm or to gene-environment interactions in susceptible individuals (30).However, there is some suggestion that treatment before 20 weeks' gestation may reduce the risk of PTB (31).

Probiotics products can be used as adjuvant therapy for bacterial vaginosis, treatment for preventing recurrence, with no adverse outcomes, but data are limited (32).

Discussion

Preterm birth is the leading cause of neonatal morbidity and mortality worldwide. While the etiology is not fully understood, intrauterine infection may account for 25%–40% of preterm deliveries (33).It also found that early BV, around the end of 1st trimester, increased the risk of spontaneous abortion (34). G. vaginalis and Prevotella spp. are high risk factors for intra-amniotic infections (29). It has been shown that the host immune response to Atopobium vaginae, a bacterial vaginosis-associated bacteria, results in the release of HIV-enhancing factors (35).

BV is most likely a polymicrobial disease dominated by anaerobes that produce a biofilm. Since anaerobic bacteria are very difficult to culture, sequencing techniques employed by microbiome profiling provide an innovative method of identifying other key culprits other than G. vaginalis, this furthering our understanding of BV and creating treatments to prevent its well-known sequelae (3).

Data indicates that antibiotics given to pregnant women reduced this overgrowth of bacteria, but did not reduce the numbers of babies who were born too early. These babies can suffer from problems related to their immaturity both in the weeks following birth such as breathing difficulty, infection and bleeding within the brain as well as problems when growing up such as poor growth, chronic lung disease and delayed development. (36).

Probiotic seems to be useful in hindering bacteria growth especially after antibiotic therapy; therefore this intervention may be considered a new prophylactic treatment for preventing recurrence of BV, in particular in high-risk patients (37).

Conclusion

BV is probably the commonest cause of abnormal vaginal discharge seen in primary care, and is certainly underdiagnosed and frequently misdiagnosed (38). Continued controversy concerning the pathogenesis of BV has led to a lack of progress in prevention and management of this infection (39).BV has been linked to a growing list of obstetric and gynecologic infections, and has been shown to increase susceptibility to HIV infection in women as well as transmission of HIV to male partners(40).Future information will enable a more personalized, more effective treatment of BV and ultimately help to prevent adverse sequelae associated with this highly prevalent disruption of the vaginal microbiome, and it will drive the development of better diagnostic tools for use in the differential diagnosis of BV(14).

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