



The influence of bacterial vaginosis on gestational week of the completion of delivery and biochemical markers of inflammation in the serum

Uticaj bakterijske vaginoze na nedelju završetka porođaja i biohemijske markere inflamacije u serumu

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Abstract

Background/Aim. Preterm delivery is one of the most common complications in pregnancy, and it is the major cause (75–80%) of all neonatal deaths. Bacterial vaginosis predisposes to an increased risk of preterm delivery, premature rupture of membrane and miscarriage. In this syndrome normal vaginal lactobacilli, which produce protective H₂O₂ are reduced and replaced with anaerobic, gram-negative bacteria and others. The aim of this study was to evaluate the influence of bacterial vaginosis on the week of delivery and biochemical markers of inflammation in the serum. **Methods.** A total of 186 pregnant women were included into this study, between the week 16 and 19 of pregnancy. In the study group there were 76 pregnant women with diagnosed bacterial vaginosis by the criteria based on vaginal Gram-stain Nugent score and Amsel criteria. In the control group there were 110 healthy women with normal vaginal flora. Ultrasound examination was performed in both groups. Vaginal fluid and blood samples were taken to determine biochemical markers with colorimetric methods. **Results.** The week of delivery was statistically significantly shorter in the study group and the levels of biochemical markers of inflammation (C-reactive protein and fibrinogen in the serum) were statistically significantly higher in women with bacterial vaginosis comparing to the control group. Also the levels of uric acid and white blood cells in the serum were higher in the study group compared to the control one. **Conclusion.** Our study indicates that the pregnancy complicated with bacterial vaginosis ends much earlier than the pregnancy without it. Also, higher levels of biochemical markers of inflammation in the serum in the study group, similarly to results of other studies, suggest that pathophysiological processes responsible for preterm delivery can begin very early in pregnancy.

Key words:

pregnancy; vaginosis, bacterial; premature birth; risk factors; biological markers.

Apstrakt

Uvod/Cilj. Prevremani porođaj predstavlja jednu od najčešćih akušerskih komplikacija, i kod 75–80% slučajeva uzročnik je neonatalnog mortaliteta. Bakterijska vaginoza smatra se značajnim faktorom rizika od prevremenog porođaja, prevremene rupture plodovih ovojnica i pobačaja. Nastaje kao posledica redukcije laktobacila koji proizvode protektivni H₂O₂, sa preovladavanjem anaerobnih, gram-negativnih i drugih nepovoljnih bakterija. Cilj ovog rada bio je da se utvrdi da li bakterijska vaginoza kod trudnica ima uticaja na nedelju završetka porođaja kao i na biohemijske markere inflamacije u serumu. **Metode.** Studija je obuhvatila ukupno 186 trudnica, između 16. i 19. nedelje gestacije. Ispitanice su bile podeljene na grupu sa dokazanom bakterijskom vaginozom po Amselovim i Njudžentovim kriterijumima (n = 76) i kontrolnu grupu sa normalnom bakterijskom florom (n = 110). Svim trudnicama je urađen ultrazvučni pregled, uzet bris vaginalnog sekreta i uzorak krvi za određivanje biohemijskih markera inflamacije kolorimetrijskim metodama. **Rezultati.** Nedelja završetka porođaja bila je statistički značajno kraća kod trudnica sa bakterijskom vaginozom u odnosu na kontrolnu grupu, dok su biohemijski markeri inflamacije, C-reaktivni protein i fibrinogen, bili statistički značajno viši u ispitivanoj grupi nego u kontrolnoj grupi. Takođe, vrednosti mokraćne kiseline i ukupnih leukocita bile su više u ispitivanoj u odnosu na kontrolnu grupu. **Zaključak.** Naša istraživanja ukazuju na znatno raniji završetak porođaja kod trudnica sa bakterijskom vaginozom, kao i na to da više vrednosti biohemijskih markera inflamacije u serumu ispitivane grupe, slično drugim istraživanjima, sugerišu da se patofiziološki procesi odgovorni za prevremeni porođaj mogu javiti vrlo rano u trudnoći.

Ključne reči:

trudnoća; vaginoza, bakterijska; porođaj, prevremeni; faktori rizika; biološki pokazatelji.

Introduction

Bacterial vaginosis (BV) presents the adverse of vaginal ecosystem, which results in decreasing or complete disappearance of hydrogen-peroxyde producing lactobacillus and enormous increase of anaerobic facultative bacteria which are 100 to 1,000 more than usual¹⁻⁴. In non-pregnant women BV increases risk of pelvic inflammatory disease (PID), postabortional PID, postoperative infections and pathological cervical changes, while in pregnancy there is higher frequency of premature rupture of membranes (PROM), preterm delivery, chorioamnionitis or postpartal endometritis. It is assumed that BV is present in 30% of pregnant women^{4,5}. In the last 20 year, extensive studies indicated close relationship between BV and preterm delivery, which presents one of the most important causes of perinatal morbidity and mortality⁶⁻⁹. The exact mechanism of BV leading to preterm delivery is still unknown, considering that its main feature is the absence of signs of inflammation, low production of cytokines and the absence of inflammatory cells such as macrophags and neutrophils⁸⁻¹⁰. However, meta-analyses indicate that as soon as BV is diagnosed [< 20 gestational weeks (GWs)] the risk of preterm delivery is increased¹¹⁻¹³. It is assumed that the risk of preterm delivery is associated with the type of vaginal flora and also with the type of immune answer that controls inflammatory process whose background could be found in genetic explanations. The attitude of some authors^{5, 10, 14} is that asymptomatic pregnant women with previous premature deliveries or abortions in second trimester of pregnancy, should control, and, in case of occurrence of subjective complaints, cure with vaginalets, and, in case of positive bacterial smears, systemic antibiotic therapy should be applied.

The aim of this study was to determine a connection between BV and the week of delivery completion, and also to investigate if early detected BV (< 20 GW) can affect biochemical markers of inflammation in the serum, in order to evaluate the pathophysiological pathways by which BV leads to preterm delivery.

Methods

This prospective study was conducted in the Department of Gynecology and Obstetrics, Clinical Center of Vojvodina, Novi Sad. The study included 198 pregnant women in total who agreed to participate in research, and they confirmed it with their signature in accordance with the Helsinki Declaration. The protocol was approved by the Ethics Committee of the Medical Faculty in Novi Sad and Clinical Center of Vojvodina, Novi Sad, Serbia.

All the pregnant women included in the research (gestational age between the GW 16 and 19 had an ultrasound examination to assess gestational age, fetal growth and development and viability of fetus. After that swabs of vaginal secretion and blood samples were taken. All the pregnant women were included in the study and monitored until the end of pregnancy.

All the participating women were divided into two groups: the study group ($n = 80$) consisted of pregnant wom-

en with BV diagnosed by the Amsel (score ≥ 3) and Nugent criteria (score ≥ 7)^{15, 16}, and the control group of pregnant women with normal vaginal flora. Pregnant women with the diagnosed intermediate vaginal flora were excluded from the research. During monitoring 12 women in total were excluded from the research. One pregnant woman had a spontaneous abortion in GW 17, one woman in GW 22 was diagnosed with fetal anomalies, and one pregnant woman had preterm delivery due to oligohydramnion. Total of 9 pregnant women were excluded due to inability of monitoring (or did not appear in Clinical Center of Vojvodina or we could not get information by telephone). Finally, the control group included of 110 pregnant women, and the study group included 76 pregnant women. Other factors that could lead to preterm delivery were the criteria for exclusion of pregnant women from the research. These factors were: multiple pregnancy, polyhydramnion, placenta praevia, diseases of mother and fetus (diabetes, hypertension, preeclampsia, eclampsia, kidney and heart diseases of mother, urinary infections, genetic malformations of fetus, intrauterine growth retardation), the local factors: anatomical malformations of uterus and vagina, cervical insufficiency, other genital infections, uterine tumors, then all diseases that can affect the level of biochemical markers in the serum such as autoimmune diseases and hormone disbalance, and also pregnant women younger than 18 and use of antibiotics just before conception and during pregnancy.

Vaginal swab was taken from lateral wall of vagina and used to create direct preparation stained by Gram and scored by Nugent method and Amsel method for diagnosis of BV¹⁴⁻¹⁶.

Hematological parameters were determined on an automatic hematological analyzer ABX Micros CRP200 (HoribaABX Diagnostics). On the same machine concentration of C-reactive protein (CRP) was determined by nephelometric method.

Glucose in the serum was determined by the enzyme referent method with hexokinase with commercial reagent (Roshe Diagnostics) on a biochemical analyzer Cobas Integra 400 plus. Uric acid was determined by the enzyme colorimetric method with uricase and peroxidase with commercial reagent (Roshe Diagnostics) on a biochemical analyzer Cobas Integra 400 plus.

Fibrinogen concentration was determined on a BFT II Fibrintimer (Siemens Health Care Diagnostics) with a modified method by Klaus with Multifibren U-reagent.

Statistical analysis was done by statistical package SPSS (ver.13) for Windows, and p value less than 0.05 were considered statistically significant. Student's t -test and Mann-Whitney test were used to compare variables between the two groups.

Results

The study included 76 pregnant women of the study group, aged between 20 and 41, and 110 pregnant women of the control group, aged between 19 and 42. Table 1 shows characteristics of all the pregnant women included in the re-

Table 1
Age of pregnant woman, gestational week (GW) during swab sample taking and the week of pregnancy completion (CW)

Parameter	Study group (n = 76)	Control group (n = 110)	p
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
Age (years)	31.47 ± 5.51	31.44 ± 5.86	0.974
GW	17.50 ± 0.808	17.41 ± 0.670	0.489
CW	37.72 ± 3.948	39.59 ± 1.06	< 0.001*

*Statistically significant difference.

search. There was a statistically significant difference between the groups in the week of completion of pregnancy ($p < 0.001$), while there was no statistically significant difference between the age and the weeks of gestation during swab sampling.

Table 2 shows percentage ratio of vaginal deliveries (VG) and Cesarean sections (CS) in the study and the control group.

Table 2
Mode of delivery

Group	Mode of delivery		Total
	VG	CS	
Control, n (%)	85 (77.1)	25 (22.9)	110 (100)
Study, n (%)	57 (75.0)	19 (25.0)	76 (100)
Total, n (%)	142 (100)	44 (100)	186 (100)

VG – vaginal delivery; CS – Cesarean sections.

Table 3 shows comparison of the mean values of uric acid, glucose, CRP, fibrinogen and hematological parameters in blood between the study and the control group. The values of CRP and fibrinogen were statistically significantly higher in pregnant women with BV compared to the control group ($p < 0.001$).

“Why is BV detected in early pregnancy more associated with preterm delivery than the one diagnosed later in pregnancy?”^{21–24}. It is assumed that one of the main factors that makes finding the answers to these questions difficult, lies in the name of the syndrome “vaginosis” and not vaginitis which explains that there is the absence of vaginal inflammatory process^{2, 19}. It is assumed that there are several factors that can individually or jointly increase the risk of preterm delivery. Microorganisms that cause BV can ascendantly spread from lower parts of genital tract to upper parts and lead to chorioamnionitis, a preterm rupture of fetal membranes and preterm delivery^{3, 25, 26}. Then, microorganisms can produce proteolytic enzymes that increase epithelium permeability in vagina, and allow passage of very pathogenic microorganisms^{27, 28}. Results of other researches indicate the role of local immunological factors, genetically predisposed and depending on their presentation to microorganisms causing BV, local inflammatory mediators such as cytokines, chemokines, and growth factors that determine what kind of consequences will appear. It is also assumed that the increased production of local cytokines-prostaglandins, can trigger preterm delivery^{29–32}.

Table 3
Mean values of hematological parameters, C-reactive protein (CRP), fibrinogen, uric acid and glucose

Variables	Study group (n = 76)	Control group (n = 110)	p
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
Uric acid ($\mu\text{mol/L}$)	170.43 ± 110.81	150.33 ± 96.84	0.520
Glucose (mmol/L)	2.99 ± 1.71	2.83 ± 1.82	0.768
CRP (mg/L)	7.07 ± 6.93	2.60 ± 1.50	< 0.001*
Fibrinogen (g/L)	4.44 ± 0.52	4.12 ± 0.36	< 0.001*
Leucocytes ($\times 10^9/\text{L}$)	8.75 ± 1.69	8.14 ± 1.75	0.129
Erythrocytes ($\times 10^{12}/\text{L}$)	3.96 ± 0.42	4.04 ± 0.41	0.408
Thrombocytes ($\times 10^9/\text{L}$)	225.57 ± 52.73	204.91 ± 53.61	0.098
Hemoglobin (g/L)	114.80 ± 9.19	118.63 ± 13.78	0.151

*statistically significant difference.

Discussion

BV is a syndrome resulting in a significant reduction of lactobacilli necessary for the creation of H_2O_2 , which enables propagation of *Gardanella vaginalis*, *Mycoplasma hominis*, anaerobes etc.^{17–20}. There is no doubt that BV and preterm delivery are associated. Currently, a number of studies have been aimed at finding answers to questions: “What are pathophysiological mechanisms linking BV and preterm delivery?”, and “Why are a large number of pregnancies, regardless of whether BV is diagnosed by clinical or microscopic methods, spontaneously resolved without consequences for mother or child and only 10–15% have a premature birth?”,

Metronidazole is the drug of choice for bacterial vaginosis. However, application of imidazole derivatives in pregnancy is still debatable, although recent studies indicate that there is no evidence of teratogenicity of this drug; it is still necessary to estimate the maternal benefit in relation to fetal-neonatal risk⁶. It has been shown that treatment with metronidazole in a dose of 400 mg 2 times a day for 5 days, and of 500 mg 2 times a day for 7 days, is more effective than giving 2 g in a single dose. Intravaginal metronidazole gel (0.75%) and clindamycin intravaginal cream (2%) have similar efficiency, because theoretically metronidazol is less active to lactobacilli than clindamycin, while clindamycin is more active to the most of the bacteria

that are related to BV³³. However, peroral application of clindamycin can be accompanied with appearance of maternal pseudomembranous colitis, which is more often in pregnant than in non-pregnant women. Application of 2% clindamycin vaginal cream one time a day is suggested, while in second and third semester of pregnancy such women can apply antibiotic therapy with: 500 mg metronidazol 2 times for 7 days, or 400 mg metronidazol 2 times for 2 days (if necessary, repeat after 4 weeks) and 250 mg of metronidazol i 333 mg erythromycina 3 times for 7 days. The treatment reduces the incidence of preterm delivery in pregnant women with increased risk (history of preterm deliveries in previous pregnancies)³³. A group of authors³³ from Medical Faculty in Wrocław, Poland, in their research from 2006 determined the importance of using hydrophilic vaginal tablets containing complex of lactic acid and Eudragit E-100. It turned out that these vaginal tablets are very useful in therapy of symptoms of BV in pregnant women. During the therapy there were no side effects, and after the therapy vaginal mucosa did not show signs of irritation or allergic reactions³⁴⁻³⁶.

The results of our study agree are in accordance with those in the literature^{1, 7, 16, 28}. There is a statistically significant difference in week of pregnancy completion in women with BV compared to women with normal vaginal flora,

while the serum levels of biochemical markers of inflammation, CRP and fibrinogen, also show statistically significantly higher values in the study group than in the control one. The values of uric acid and total number of leukocytes are higher in the study than in the control group. There is also a higher number of Cesarean deliveries in the group with BV than in the control group.

Conclusion

The results of our study indicate a significantly earlier delivery in pregnant women with the diagnosed bacterial vaginosis in early pregnancy, and also statistically significantly higher values of C-reactive protein and fibrinogen in pregnant women with bacterial vaginosis, that can help in further research with both existing and possible new markers, which could help in clarification of pathogenetic mechanisms which link bacterial vaginosis and preterm delivery, as well as in identification of women with the risk of preterm delivery caused by infection, at the same time. However, it is also necessary to expand existing researches and include genetic analysis, i.e. examine the response of genotype and immunologically different phenotypes in dependence on change of microenvironment or inflammation, in order to explain pathophysiology of preterm delivery.

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