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COMPLICATIONS ASSOCIATED WITH BACTERIAL VAGINOSIS

SUMMARY

Bacterial vaginosis (BV) is a change in vaginal ecosystem where lactobacilli dominate, normal flora is absent or greatly reduced, and replaced with a mixed, predominantly anaerobic flora, consisting of Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus spp, Bacteroides spp, Prevotela spp, Peptostreptococcus spp, Fusobacterium spp and Porphyromonas spp.

The four studies, conducted and published in the United States, Africa and Thailand, have all shown that women having bacterial vaginosis have a higher prevalence of HIV. Most epidemiological studies have found a "dose-response" relation in which increasingly abnormal flora or severe BV is associated with increasing risk of HIV. Understanding this "dose-response" relation will help clarify why BV enhances HIV transmission. Again, it was found in the multi-variant model that women without lactobacilli were 70% more likely to get gonorrhea and other STD. BV may lead to an increased risk of salpingitis and/or endometritis, postsurgical infections (e.g. postcesarean endometritis, posthysterectomy vaginal cuff cellulitis), and adverse outcomes in pregnancy, including premature rupture of membranes, premature labor, and chorioamnionitis. In addition, there is a possibility that bacterial vaginosis is in some way associated with the development of cervical intraepithelial neoplasia. Furthermore, there are some indications that correlate BV with cytologic inflammatory changes noted on the cervix.

The association of BV with numerous obstetric and gynecologic complications requires a compulsory screening and treatment of BV in different clinical conditions. Additional investigations of this disease must include prevention of complications in pregnancy as well as the treatment of BV in non-pregnant women.

Key words: **bacterial vaginosis, female genital tract infections, HIV infection, CIN, preterm delivery**

INTRODUCTION

Bacterial vaginosis (BV) is a change in vaginal ecosystem where lactobacilli dominate, normal flora is absent or greatly reduced, and replaced with a mixed, predominantly anaerobic flora, consisting of Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus spp, Bacteroides spp, Prevotela spp, Peptostreptococcus spp, Fusobacterium spp and Porphyromonas spp (1). The criteria for diagnosing bacterial vaginosis include: looking for clue cells on a wet mount, evaluating vaginal pH, looking

at the discharge and testing for amine odor. These are the so-called Amsel criteria. Although little progress has been made to identify the causal factor, the pathophysiology of this syndrome was clearer. Although symptoms are quite recognizable, obstetric and gynecologic complications continue to increase in number (2).

The Centers for Disease Control and Prevention (CDC), which is a part of the principal agency in the United States government for protecting the health and safety of all Americans and for providing essential human services, have recently included bacterial vaginosis on their list of emerging infectious diseases (3). Bacterial vaginosis has been well-known for the last 100 years. Although the disease is quite common, it is not known to be increasing. There are four reasons why BV has been added to the list of emerging infectious diseases: bacterial vaginosis is widely recognized as a cause of adverse pregnancy outcomes. This common vaginal condition is associated with an increased risk of HIV in women. There is an increasing awareness that bacterial vaginosis is not routinely recognized by either women or their health care providers; and finally, there is a recognition that treatments are not always successful (in 1 of 5 women the condition will recur one month after the treatment) (3).

BV may lead to an increased risk of salpingitis and/or endometritis, postsurgical infections (eg, postcesarean endometritis, posthysterectomy vaginal cuff cellulitis), and adverse outcomes in pregnancy, including premature rupture of membranes, premature labor, and chorioamnionitis. There is a possibility that bacterial vaginosis is in some way associated with the development of cervical intraepithelial neoplasia (4).

BACTERIAL VAGINOSIS AND HIV

Several factors could lead to the acquisition of HIV when the normal vaginal microflora is disturbed (5, 6). Firstly, depletion of lactobacilli may limit production of hydrogen peroxide and other antibacterial activities, which are protective against potentially pathogenic organisms such as STDs and possibly HIV. Secondly, low vaginal pH has been postulated to inhibit CD4 lymphocyte activation and reduce HIV target cells in the vagina. Therefore, the lack of lactic acid production by lactobacilli could lead to an elevated pH which may be more conducive to growth and survival of the virus. Thirdly, similar to the experience with several bacteria, elevated vaginal pH may enhance HIV adherence to vaginal eukaryotic cells (7).

The four studies, conducted and published in the United States, Africa and Thailand, have all shown that women having bacterial vaginosis have a higher prevalence of HIV (6). The results of the study conducted in Thailand, which included 144 women, pointed to a threefold increased risk of HIV among women with BV. In the study conducted in Uganda, which included 4,718 pregnant and non-pregnant women from rural areas, it was shown that women with bacterial vaginosis had a twofold increased risk of HIV. In the next study conducted in Africa (Malawi), it was shown that in 9,126 pregnant women with BV, there was a twofold increased risk of HIV (7). The study from North Carolina showed that in 724 women (from rural areas) with bacterial vaginosis, there was a fourfold increased risk of HIV. These studies, like many others, confirm that in the population affected with BV, there is a great risk of HIV (8, 9).

Most epidemiological studies have found a "dose-response" relation in which increasingly abnormal flora or severe BV is associated with increasing risk of HIV. Understanding this "dose-response" relation will help clarify why BV enhances HIV transmission (10).

Taha et al. showed in the study published 7 years ago that women having bacterial vaginosis were 3 $^1/_2$ times more likely to become HIV positive by the time of delivery when compared to women without bacterial vaginosis. He also found that women with gonorrhea and syphilis were at increased risk of HIV seroconversion. However, trichomoniasis was not significantly associated with becoming HIV seropositive. The risk of bacterial vaginosis, syphilis, and gonorrhea was similar, but because BV was more prevalent, it was more influential in transmission than these two classical STDs (7). Again, in the multi-variant model, it was found that women without lactobacilli were 70% more likely to get gonorrhea and other STDs (11).

BACTERIAL VAGINOSIS AND FEMALE GENITAL TRACT INFECTIONS

Moi and Paavonen pointed that up to 50% of women with cervicitis had bacterial vaginosis (12, 13, 14). Numerous studies have shown an association of BV with mucopurulent endocervicitis (MPC) (13, 14). Up to 50% of women attending sexually transmitted disease clinics and diagnosed with MPC have coexistent BV (12). Preliminary data by Schwebke et al. suggest the need to treat coexistent BV in women with MPC. Failure to do so resulted in an excess rate of persistent MPC, 47% in the BV-untreated group compared with 14% in the BV-treated group (15).

Additional supporting evidence is offered by the observation that BV is associated with inflammatory changes noted on cervical cytology. It appears from this minor study that when you see cervicitis you should at least consider screening those women for bacterial vaginosis (15).

BV appears to be a risk factor for endometritis and is commonly found in women with both clinical diagnosis of pelvic inflammatory disease (PID) and confirmed salpingitis. The first link between bacterial vaginosis and pelvic inflammatory disease was described 17 years ago by Dr David Eschenbach in the American Journal of Obstetrics and Gynecology (16). In this study, which was a cross-sectional look at women attending a sexually transmitted disease clinic, they found that 8 of 311 women or 3% actually had undiagnosed or clinically unrecognized pelvic inflammatory disease compared to 0 of 350 women without BV. In 1994, Soper et al. recognized that BV was present in 62% of women with laparoscopically confirmed PID (17), which virtually means that all of the anaerobic bacteria found in these women were associated with bacterial vaginosis. These are the anaerobes like Prevotella bivia, Peptostreptococcus spp and Bacteroides melaninogenicus. Actually, his inference was that a high proportion, which was about 2/3 of women with laparoscopically confirmed PID, had an evidence of anaerobic infection. Paavonen et al. from Finland found that 30% of women with histological endometritis had bacterial vaginosis compared to none of the women in which histologic endometritis was absent. Many confirmatory data support the biological plausibility that BV is a risk factor for PID (14).

BACTERIAL VAGINOSIS AND COMPLICATIONS IN WOMEN UNDERGOING GYNECOLOGIC SURGERY

BV has been associated with endometritis, PID, and vaginal cuff cellulitis after invasive procedures, including endometrial biopsy, hysterectomy, hysterosalpingography, placement of an IUD, cesarean section, and uterine curettage (18).

Sixteen years ago, Larsson et al. published a study evaluating whether or not women who had clue cells in the vagina at the time of a first-trimester pregnancy termination were more likely to develop post-abortion PID. He found that of 65 women who had clue cells in the vagina, 7 or 12% developed post-partum endometritis. Compared to only 4 of 133 cases, or 3% , did not have clue cells (18).

A study published 6 years ago by Lin et al. encompassed 175 women undergoing gynecologic surgery including vaginal hysterectomy, laparotomy, and total abdominal hysterectomy. It was shown that women with bacterial vaginosis were substantially more likely to develop postoperative infections despite either preoperative or perioperative antibiotics' administration (19). This study and many others investigations highlighted the failure of prophylactic antibiotics to prevent postoperative infections, and gives credence to idea of targeting prophylactic antibiotics for surgical patients where BV is present (19).

BACTERIAL VAGINOSIS AND ADVERSE PREGNANCY OUTCOMES

Over the past 20 years, there have been a great number of studies which have linked bacterial vaginosis with the pre-term delivery. These studies have come from the United Kingdom, United States, Finland, Jakarta, Indonesia and Australia, and have obtained the same results. The women who had bacterial vaginosis had an increased risk of pre-term delivery (20).

The women with BV also have an increased risk of pregnancy loss or miscarriage between 14–22 weeks. There are now about 3 or 4 studies which show that bacterial vaginosis is significantly associated with pregnancy loss earlier during pregnancy prior to the pre-term delivery (20). There is also little evidence showing that women with bacterial vaginosis have a threefold increased risk of amnionitis even in the second trimester. If there are no complications until the late second or early third trimester, there are data showing that women with BV have a two- to threefold increased risk of histologic chorioamnionitis (21). The organisms from the vagina can actually ascend between the chorion and amnion. And at delivery, even if there are no complications until the 37th week of pregnancy, there is a twofold increased risk of intra-amniotic infection or fever during labor and a fourfold increased risk of post-partum endometritis. BV is associated with adverse effects in the first, second and third trimester of pregnancy (22). The current theory is that these lower genital tract infections such as BV actually change the local cytokine and ephithelial cell response and alter the neutrophil or PMN response. Therefore, it is likely that both invasion and local immune response effects are important for this link (23).

BACTERIAL VAGINOSIS AND CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Evidence regarding a causal relationship between bacterial vaginosis and cervical intraepithe-

lial neoplasia has been so far incomplete and conflicting. The possibility exists that bacterial vaginosis is in some way associated with the development of cervical intraepithelial neoplasia, i.e. as a cofactor to human papilloma virus. Therefore, bacterial vaginosis must be taken in consideration in future studies on CIN (4, 23). To determine whether bacterial vaginosis is associated with cervical intraepithelial neoplasia, a retrospective study was conducted at the Genitourinary Medicine Clinic at Southlands Hospital, Shoreham-by-Sea, UK. That study has shown that an increased prevalence of cervical intraepithelial neoplasia was associated with bacterial vaginosis (24).

The study by Barrington et al. (25) has shown a statistically significant association between anaerobic vaginosis that produce amines and cervical intraepithelial neoplasia 2 and 3. It is, therefore, theoretically possible that nitrosamines may be an important agent in the development of premalignant disease of the cervix (25).

CONCLUSION

The presence of BV puts the patient at increased risk of genital tract infection, with severe consequences to fertility and outcome of pregnancy. The association of BV with numerous obstetric and gynecologic complications requires a compulsory screening and treatment of BV in different clinical conditions.

Areas for further research on BV include pathogenesis and therapy. Additional treatment studies must include methods to prevent pregnancy complications and treat BV in non-pregnant women.

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KOMPLIKACIJE NASTALE USLED BAKTERIJSKE VAGINOZE

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SAŽETAK

Bakterijska vaginoza (BV) je promena normalne vaginalne mikroflore. Normalna flora u kojoj dominiraju laktobacili je odsutna ili veoma umanjena i zamenjena mešovitom, uglavnom anaerobnom florom koja se sastoji od sledećih vrsta bakterija: Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus spp, Bacteroides spp, Prevotela spp, Peptostreptococcus spp, Fusobacterium spp i Porphyromonas spp.

Četiri studije, objavljene i izvedene u zemljama SAD-a, Africi i Tajlandu pokazale su da žene sa bakterijskom vaginozom imaju povećanu prevalencu HIV infekcije. Veliki broj epidemioloških studija pokazao je da postoji "dozno-zavisna" veza između stepena promene vaginalne flore kod BV i rizika od HIV infekcije. Razumevanje ove " dozno-zavisne" veze između BV i HIV infekcije pomaže u pojašnjavanju patogenetskog mehanizma ove komplikacije. Takođe je jednom opsežnom multi-varijantnom studijom utvrđeno da su žene bez laktobacila 70% podložnije oboljevanju od gonoreje i drugih seksualno prenosivih bolesti. Kod žena sa BV-om može doći do sledećih komplikacija: salpingitisa i/ili endometritisa, posthirurških infekcija (endometritis, posle porođaja carskim rezom, posthisterektomijski vaginalni celulitis), i lošeg ishoda trudnoće, uključujući prevremeno pucanje plodovih ovojaka, prevremeni porođaj i horioamnionitis. Postoji mogućnost da je BV na neki način povezana sa razvojem cervikalne intraepitelijalne neoplazije (CIN). Takođe, postoje podaci koji povezuju BV sa citološkim upalnim promenama na cerviksu.

Povezanost BV sa brojnim akušerskim i ginekološkim komplikacijama zahteva obavezan skrining žena i lečenje BV kod različitih drugih kliničkih stanja. Dodatna istraživanja ove bolesti moraju uključiti i pronalaženje načina sprečavanja komplikacija u trudnoći, kao i postupka izlečenja BV kod žena koje nisu gravidne.

Ključne reči: **bakterijska vaginoza, infekcije genitalnog trakta žena, HIV infekcija, CIN, prevremeni porođaj**