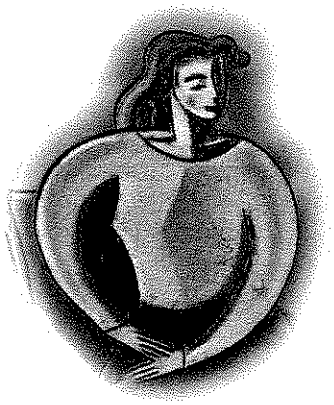
Women's Health Care
A PRACTICAL JOURNAL FOR NURSE PRACTITIONERS



BACTERIAL VAGINOSIS: DIAGNOSIS AND TREATMENT UPDATE

by Leia Raphaelidis, FNP, BC and
R. Mimi Clarke Secor, MS, MEd, APRN, BC, FNP, FAANP

Bacterial vaginosis (BV) is a common, complex, and potentially serious vaginal infection. This article provides up-to-date information regarding pathophysiology, risk factors, potential obstetrical and gynecologic complications, and recent advancements in the diagnosis and treatment of BV, including the management of recurrent BV.

Bacterial vaginosis is the most common of all vaginal infections in reproductive-aged women, with prevalence rates ranging from 5% (for women without any symptoms) to 25% (for women with gynecologic symptoms).[1] However, BV prevalence has been reported to be as high as 60% in women who attend clinics specializing in the treatment of sexually transmitted infections (STIs).[1] Although the cause of BV is still unknown, progress has been made in terms of understanding the complex pathophysiology and associated risk factors involved in this infection. In addition, new diagnostic tests have become available, and new treatments have been developed and approved. More than a minor nuisance, BV has been linked to numerous serious gynecologic and obstetric complications. Therefore, nurse practitioners (NPs) need to be fully informed about this complex, often subtle, and all-too-common vaginal infection.

BV accounts for up to half of all office visits for vaginal complaints.[2] BV typically manifests with an increased, thin, milky vaginal discharge and a sharp or fishy odor that some women may find distressing. Vaginal irritation and itching are uncommon. About 50% of women with BV are asymptomatic; thus, the diagnosis may come as a surprise to many of them.[3]

Because BV may appear after beginning a new sexual relationship, many women think that they have contracted an STI. However, BV is thought to be *associated* with sex but not *transmitted* by sex. The precise relationship between BV and sex has not been established. From an epidemiologic standpoint, BV "acts" like an STI, in that it frequently develops after a woman has sex with a new partner.[4] But studies investigating the treatment of male partners have failed to show benefit in terms of reducing BV recurrence rates, providing evidence that BV is *not* sexually transmitted.[5,6]

Some women self-diagnose BV as a yeast infection and self-medicate with over-the-counter (OTC) antifungal creams. They seek care from their healthcare provider when symptoms fail to resolve. Self diagnosis of vaginal symptoms is frequently inaccurate and should be discouraged.[7]

Unfortunately, many women experience recurrent episodes of BV, and are all too familiar with the symptoms. They may even present to the office saying, "My BV is back," and in many cases, they are correct. BV can be frustrating for NPs and patients alike, because the risk of recurrence is high, ranging from 30% at 1 to 3 months post-treatment to 70% at 3 to 9 months post-treatment.[8]

Furthermore, BV is associated with a range of STIs, including herpes simplex virus infection, human papillomavirus infection, gonorrhea, and chlamydia. Of great concern is recent worldwide research indicating that BV is a risk factor for human immunodeficiency virus (HIV) infection; that is, the presence of BV may increase a woman's risk of acquiring and transmitting HIV.[9-11]

Finally, BV is associated with an increased risk of post-gynecologic surgery infection; endometritis; pelvic inflammatory disease (PID), including subclinical PID; cervicitis; cystitis; and adverse pregnancy outcomes, including low birth weight, premature rupture of membranes, preterm birth, and postpartum infections.[9,11-14] Research has shown that treating BV with metronidazole before surgical abortion significantly reduces the risk of postoperative PID.[15] Similarly, treating BV before a woman has gynecologic surgery has been reported to significantly reduce the risk of postoperative infections.[16]

NORMAL VAGINAL ECOSYSTEM AND THE SHIFT IN VAGINAL FLORA

A healthy vagina is colonized by a predominance of lactic acid- and hydrogen peroxide-producing, estrogen-dependent lactobacilli. These lactobacilli maintain the normal acidic vaginal pH (pH range, 3.8-4.5) and act as a defense against pathogens and genital infections. BV is characterized by the *absence* of protective lactobacilli and a 100- to 1000-fold *overgrowth* of facultative and anaerobic bacteria.[11,17] Although clinicians tend to think of *Gardnerella vaginalis* as the pathogen most often associated with BV, more than 35 different bacteria have been identified and associated with BV.[18]

Researchers now have a better understanding of the pathophysiology of BV, but the cause of BV has not yet been identified.[18] Researchers do not know whether the absence of lactobacilli leads to overgrowth of anaerobes or whether the increased anaerobes displace the lactobacilli, or whether other unidentified causes are involved.[17] Recent discovery of 16 new bacterial species, including 3 bacteria in the Clostridiales order (BV-associated bacteria 1, 2, and 3), *Atopobium vaginae,* 9 *Prevotella*-related bacteria, and others, may clarify the etiology. In fact, a new theory based on recent research findings suggests that the metabolic interaction of numerous bacterial species may cause this complex polymicrobial infection.[18] It is also possible that this new research may contribute to the development of more effective diagnostic and therapeutic approaches.[18]

BV accounts for up to half of all office visits for vaginal complaints.

Risk factors for BV include having a recent new sexual partner (male or female), having multiple partners, engaging in oral sex, vaginal douching, and having a black racial background.[19-25] Recent research has identified increased psychosocial stress as a significant independent risk factor for BV.[26] Increased stress seems to be associated with new infections but does not seem to significantly influence chronic infections.[26] Young, sexually active women are most likely to be diagnosed with BV, but this infection may affect women throughout the reproductive years.[17] BV may resolve spontaneously, although the exact rate of spontaneous resolution is unknown.[27]

BV is referred to as "vaginosis" rather than "vaginitis" because it is not usually associated with classic inflammatory symptoms of vulvar pruritus and/or irritation. However, according to recent research, BV is an inflammatory condition associated with the production of cytokines that may be responsible for increasing the risk of acquiring and transmitting various STIs.[28] BV is also associated with a reduction in secretory leukocyte protease inhibitor levels, which might provide an additional explanation as to why HIV may be more easily acquired and transmitted by women with BV.[28,29]

Overgrowth of anaerobic bacteria in the vagina leads to increased release of amines, resulting in the hallmark sign of BV—a fishy odor. These amines break down mucins, which accounts for the increased, thin, milky vaginal discharge.[17] Women may report that the odor is more noticeable after unprotected intercourse or dur-

ing menses; this observation is related to the volatilization of the amines associated with these more alkaline environments.

MAKING THE DIAGNOSIS

In the examination of a woman with BV, the external genitalia typically appear normal, although in some cases, vaginal discharge coats the vulva or pools at the posterior fourchette. The speculum examination usually reveals a homogeneous, thin, adherent, milky-white vaginal discharge. A sharp or fishy odor may be noted during the examination, even prior to amine testing. The cervix usually appears normal. Of importance, cervicitis may be associated with BV, and is manifested by cervical erythema, friability, and mucopus.[9] Bimanual examination findings are unremarkable unless PID or endometritis is also present. In these cases, NPs may note associated tenderness on palpation of the uterus and/or adnexae.

For more than 20 years, it has been recommended that the clinical diagnosis of BV be made by identifying the presence of at least three of four Amsel's criteria:[8,17]

- Homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- pH of vaginal discharge that is greater than 4.5;
- Positive amine or "whiff" test before or after mixing 10% to 20% potassium hydroxide with a sample of vaginal discharge (a sharp or fishy odor is released); and
- Presence of "clue cells" (epithelial cells coated with bacteria obscuring the cell borders) on microscopic examination of a saline sample of vaginal secretions; this procedure is also referred to as a wet mount or a wet prep.

Of these four criteria, the most reliable combined predictors of BV are the presence of clue cells and a positive amine test result.[17] Vaginal pH alone should *not* be used as a single criterion for diagnosing BV because many factors can raise vaginal pH, including *Trichomonas vaginalis* infection; other STIs; cervical mucus, blood, or semen; a foreign object in the vagina; or a low-estrogen state such as that occurring postpartum or menopausally or in women using injectable medroxyprogesterone acetate (Depo-Provera® or depo-subQ provera 104™). To ensure maximum accuracy in assessing Amsel's criteria, NPs need to know how to perform the diagnostic tests correctly.[16,30]

Vaginal cultures for *G vaginalis* are not helpful in diagnosing BV because this pathogen is often part of normal vaginal flora; therefore, a positive culture finding is non-specific.[16,25] The Pap smear is of variable usefulness. Although the Pap test finding may be read as "predominance of coccobacilli consistent with a shift in vaginal flora," it is only 55% sensitive in diagnosing BV.[31]

Recently, the US Food and Drug Administration (FDA) approved two point-of-care office diagnostic kits for BV, both of which are CLIA (Clinical Laboratories Improvement Act) waived and may be performed in the outpatient office setting. The OSOM® BVBLUE test, sold by Genzyme Diagnostics, has greater than 90% sensitivity and takes 10 minutes to perform. This test may be used in lieu of vaginal microscopy if a microscope is unavailable. Formerly known as the FemExam®, the QuickVue Advance® pH and Amines test, sold by Quidel, is approximately 90% sensitive and takes about 2 minutes to perform. Both the OSOM® BVBLUE test and the QuickVue Advance® pH and Amines test are reimbursed by insurance.

INDICATIONS FOR TREATMENT

BV treatment indications are addressed in the 2006 Sexually Transmitted Diseases Treatment Guidelines of the Centers for Disease Control and Prevention (CDC).[25] According to the CDC, indications for BV treatment in non-pregnant women include (1) relief of vaginal symptoms and signs of infection and (2) reduction of infectious complications after abortion or hysterectomy.[25] Other potential benefits of treatment include a reduction in risk for other STIs, including HIV.[25] Finally, the CDC restates that all women with symptomatic BV require treatment.[25]

Although the new 2006 CDC guidelines state that more information is needed before recommending treatment of asymptomatic BV before certain invasive gynecologic procedures are performed, some clinicians and researchers routinely screen and treat women for BV prior to performing endometrial biopsy, insertion of an intrauterine device, or endometrial curettage.

Despite the numerous STIs associated with BV, no data support the treatment of asymptomatic BV or the supposition that BV treatment reduces the risk of STI

comorbidities.[4] Even so, some researchers recommend screening for and treating both asymptomatic and symptomatic BV in an effort to promote normal vaginal flora and to reduce the risk of STIs and other associated obstetric and gynecologic complications.[25,32]

BV in pregnancy has been associated with a range of adverse pregnancy outcomes, including premature rupture of membranes, preterm labor, spontaneous abortion, preterm birth, chorioamnionitis and postpartum endometritis.[25,33,34] In pregnant women, the new CDC guidelines recommend treating BV to relieve vaginal symptoms and signs of infection. Additional potential benefits include reduction of the risk for infectious complications associated with BV in pregnancy and reduction of the risk for other STIs, including HIV.

For pregnant women, research has shown that treating BV in those who are at high risk for preterm delivery may reduce the rate of preterm delivery. Therefore, the CDC advises that clinicians consider screening for asymptomatic BV in these high-risk pregnant women at the first prenatal visit.[25] Furthermore, high-risk women in whom BV is diagnosed and treated should undergo a follow-up evaluation 1 month later to determine whether therapy has been effective.[25] Because of the potential obstetric complications associated with untreated BV, some experts recommend that all pregnant women be screened for BV early in pregnancy regardless of their risk or symptom status.[35,36]

Pre-2002 studies that had sought to determine the usefulness of treating asymptomatic BV in women with an uncomplicated pregnancy reported either no clear benefit of treatment or conflicting results.[37,38] By contrast, several studies since 2002 have reported improved pregnancy outcomes associated with treatment of BV in pregnancy.[35,39,40] These studies utilized oral[35] or vaginal[39,40] clindamycin and screened and treated women in the first half of pregnancy, which, according to the researchers, is the likely reason for the different (ie, favorable) findings. In fact, several of these researchers advocate BV screening and treatment as early in pregnancy as possible to reduce adverse pregnancy outcomes.

Treatment of male sexual partners of patients with BV has not been shown to reduce the recurrence of BV; thus, such treatment is not recommended.[25] Because there is a high concordance of BV in women having sex with women, female partners of women with BV should be clinically evaluated for BV and treated if necessary.[20]

TREATMENT OPTIONS

Two medications, metronidazole and clindamycin, are used to treat BV. All of the CDC's 2006 STD Treatment Guidelines' recommended and alternate regimens are listed in the Table.[25]

Metronidazole—The 14-dose oral metronidazole regimen (Flagyl®) and the 5-dose metronidazole vaginal gel regimen (MetroGel-Vaginal®) are considered equally effective, with a cure rate exceeding 90% at 1 week.[17] Both medications are available in generic versions. NPs may be tempted to prescribe the 2-g stat oral dose of metronidazole that appeared in previous CDC guidelines because it is less expensive and lends itself to better patient adherence. However, the efficacy of this regimen is significantly less than that of the regimens currently recommended by the CDC and is therefore no longer recommended by the CDC.[25,41,42]

Common side effects of oral metronidazole include nausea (sometimes with vomiting) and abdominal pain; metallic taste and headache may also occur. The substantially lower dose of intravaginal metronidazole, when compared with the oral version of this agent, may have fewer systemic side effects, but many adolescents and some women find the intravaginal route of administration less acceptable. Patients who are using oral or intravaginal metronidazole must abstain from drinking alcoholic beverages because of the drug's disulfiram (Antabuse®)-like effect, which may result in severe nausea and vomiting.[43]

Clindamycin—Also recommended by the CDC as a first-line treatment for BV is clindamycin phosphate vaginal cream (Cleocin® Vaginal Cream 2%), one applicator vaginally at bedtime for 7 days. Data from several large, randomized, double-blind studies have shown that vaginal clindamycin for 7 days is as effective as oral metronidazole 500 mg twice daily for 7 days.[25,44-46] According to the new 2006 CDC guidelines, clindamycin suppositories (Cleocin® Vaginal Ovules) and oral clindamycin (Cleocin®) are considered alternative treatments.[25]

Recently, the FDA approved a single-dose vaginal clindamycin treat-

ment for BV (Clindesse™ Vaginal Cream 2%), which delivers a total dose of 100 mg of clindamycin.[47] This product utilizes a novel delivery system that is bioadhesive and time-released over a 5-day period, providing continuous therapeutic effects.[48] The product is associated with approximately 50% less leakage than conventional vaginal medications.[48] In addition, because this vaginal cream is bioadhesive, it may be inserted any time of day, not just at bedtime, thereby enhancing patient compliance and onset of therapeutic effect.[47] According to recent research, cure rates are similar for single-dose vaginal clindamycin and the 7-day regimen of vaginal clindamycin.[49]

Women using any of the intravaginal clindamycin preparations, all of which are oil based, should be cautioned that these products may weaken latex condoms; therefore, women should avoid use of latex condoms during therapy and for 5 days afterward.[47] Women using oral or vaginal clindamycin products should be warned about the risk of pseudomembranous colitis, an uncommon but potentially serious side effect.[50]

TABLE 1 2006 CDC GUIDELINES FOR THE TREATMENT OF BACTERIAL VAGINOSIS[25]

RECOMMENDED REGIMENS:

- Metronidazole 500 mg orally twice daily for 7 days OR
- Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once daily for 5 days OR
- Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

ALTERNATIVE REGIMENS:

- Clindamycin 300 mg orally twice daily for 7 days OR
- Clindamycin ovules 100 mg (one ovule) intravaginally at bedtime for 3 days

RECOMMENDED REGIMENS IN PREGNANCY:

- Metronidazole 500 mg orally twice daily for 7 days OR
- Metronidazole 250 mg orally 3 times daily for 7 days OR
- Clindamycin 300 mg orally twice daily for 7 days

OTHER REGIMENS IN PREGNANCY:

- Clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for 7 days* OR
- Clindamycin ovules 100 mg (one ovule) intravaginally at bedtime for 3 days*

*Use in first half of pregnancy only.

CDC = Centers for Disease Control and Prevention.

General Recommendations— Both metronidazole and clindamycin may cause secondary vaginal candidiasis; the risk is about 14% for either product.[51,52] Recent research suggests that both metronidazole and clindamycin are lactobacilli-sparing, and are associated with similar recolonization levels of vaginal lactobacilli at both 21 and 30 days post-treatment.[53] Abstaining from sex or using condoms during treatment and for a month afterwards may increase the chance of re-establishing normal flora and avoiding BV recurrences.[41] In addition, in vitro research suggests that some vaginal pathogens may be resistant to clindamycin, although the clinical significance of this finding is unclear.[54]

Treating BV in Pregnancy— According to the new CDC guidelines, the recommended treatment options for treating pregnant women with BV are oral metronidazole or clindamycin, either regimen for 7 days (Table).[25] Clindamycin phosphate vaginal cream is FDA-approved for use in the second or third trimester of pregnancy,[55] but the new guidelines recommend its use only in the first half of pregnancy. The use of vaginal clindamycin in pregnancy is still controversial, owing to the mixed results reported by several studies that have evaluated the use of vaginal clindamycin in pregnancy.

Recent studies conducted by Kiss et al and Lamont et al have reported a significant reduction (50% and 60%, respectively) in preterm labor in women treated *early* in pregnancy (16-17 weeks' gestation) with vaginal clindamycin as compared with placebo.[36,40] These data contributed to the CDC's recommendation to use vaginal clindamycin only in the first half of pregnancy.

Studies conducted before the 2002 CDC guidelines reported no effect or negative effects associated with vaginal clindamycin treatment in pregnancy—hence, the recommendation in these earlier guidelines to avoid vaginal therapy during the entire pregnancy. Possible explanations for these findings are that treatment was administered too late in pregnancy (ie, during the second half of pregnancy), when the infection was more advanced, or that suboptimal treatment regimens were used.

The new CDC guidelines cite one small study that demonstrated the equivalent efficacy of oral and vaginal metronidazole in the treatment of BV in pregnancy.[25,28] This study compared vaginal metronidazole one applicator at bedtime for 5 days with oral metronidazole 500 mg twice daily for 7 days.[28] This being said, however, the CDC does not make a formal recommendation regarding the use of vaginal metronidazole in pregnancy. Therefore it seems prudent to avoid prescribing this product to pregnant women or to prescribe this product cautiously until further research is completed.

NON-ANTIBIOTIC TREATMENTS FOR BV

The primary non-antibiotic treatments for BV include exogenous lactobacilli (delivered via oral formulations), acidification of the vagina (accomplished by douching with OTC acidifying preparations), and antiseptics such as OTC povidone-iodine (Betadine®) or hydrogen peroxide douching preparations. However, the results of research using these approaches have been disappointing.[52] Therefore, none of these measures can be recommended at present. Another possible strategy that may be considered for future study involves reducing or eliminating menses (lactobacilli bind to red blood cells). Future research may also be conducted to determine whether poor hygiene, thong underwear, or pubic-hair shaving plays a role in causing or aggravating acute or chronic BV.

RECURRENT BV

Although treatment trials report BV cure rates of 80% to 90% at 1 week,[56] up to 30% of women experience a recurrence within 3 months.[17] The cause of recurrent BV is not fully understood. However, possible explanations include failure to fully eradicate BV-associated bacteria,[19] re-infection from an exogenous source, and failure to achieve vaginal recolonization of protective lactobacilli.[16,18,41]

Although treatment trials report BV cure rates of 80% to 90% at 1 week, up to 30% of women experience a recurrence within 3 months.

To treat recurrent BV, one approach that has shown promise and is mentioned in the new CDC guidelines is a 4- to 6-month course of metronidazole vaginal gel.[25] Recent research has demonstrated a statistically significant but clinically modest reduction in the recurrence rate of BV during this suppressive therapy.[41,57] The regimen involves initial induction therapy consisting of one applicator of gel inserted vaginally at night for 10 days, a negative "test-of-cure" post-induction therapy, and, if cured, a suppression maintenance regimen consisting of one applicator inserted vaginally twice weekly for 4 months.[57] However, a high rate of secondary vulvovaginal candidiasis was also reported in this study. So, when prescribing this therapeutic regimen, NPs should anticipate this possibility. A high relapse rate was reported when therapy was stopped; therefore, the authors recommended that after 4 to 6 months of suppressive therapy, the medication be gradually tapered over several months in order to lessen this risk.[57]

Clindamycin vaginal cream may be effective in preventing recurrent BV, but it has not been formally studied for this indication. To date, no suppression studies have been conducted with oral antibiotics.

PATIENT EDUCATION

Few data exist regarding specific interventions with patients to decrease their risk of acquiring BV or experiencing BV recurrences. Some experts recommend that, over the course of treatment and for a month after therapy is completed, women who are having sex with a male partner should have him use a condom during each encounter.[41] Of note, regular condom use has been reported to reduce the risk of developing BV by 30% when compared with nonuse or rare use of condoms.[58] In addition, NPs should advise women to avoid douching and to practice safe sex. BV has not been associated with tampon use, although many lay sources advise against tampon use to prevent BV. NPs may also encourage women to try to reduce their psychosocial stress levels, increase sleep, follow a balanced diet, practice good hygiene, and institute other basic health-promoting interventions.

CONCLUSION

Although many recent studies have shed light on the complex nature of BV, a major knowledge gap still exists regarding the etiology, prevention, and treatment of BV, particularly in terms of managing chronic, recurrent infections. BV diagnosis is established by identifying the presence of three out of four of Amsel's criteria, including clue cells on vaginal microscopy. Two new point-of-care office diagnostic tests are available to facilitate diagnosis. First-line treatment options for BV include oral and vaginal metronidazole and vaginal clindamycin. At present, recurrence rates after initial treatment are high. Suppressive maintenance therapy for management of chronic BV is an option for women suffering from recurrent BV. ■

Leia Raphaelidis is a family nurse practitioner specializing in reproductive health at Planned Parenthood of the Southern Finger Lakes in Ithaca, New York. R. Mimi Clarke Secor is president emerita and senior advisor of NPACE (Nurse Practitioner Associates for Continuing Education) in Natick, Massachusetts, and a visiting scholar at Boston College in Chestnut Hill, Massachusetts. *Leia Raphaelidis states that she does not have a financial interest or other relationship with any commercial product named in this presentation. R. Mimi Clarke Secor serves as a speaker and consultant for Ascend Therapeutics, Digene Corporation, GlaxoSmithKline, Mission Pharmacal, 3M Pharmaceuticals, Organon USA, Duramed Pharmaceuticals Inc., a subsidiary of Barr Pharmaceuticals, Inc., Ortho-McNeil Pharmaceutical, Pfizer Inc., Procter & Gamble Pharmaceuticals, and Ther-Rx Corporation.*

REFERENCES

1. Mead PB. Epidemiology of bacterial vaginosis. *Am J Obstet Gynecol.* 1993;169:446-447.

2. Chantigian PD. Vaginitis: a common malady. *Prim Care.* 1988;15(3):517-547.

3. Amsel R, Totten PA, Speigal CA, et al. Non-specific vaginitis: diagnostic and microbial and epidemiological associations. *Am J Med.* 1983;74:14-22.

4. Schwebke JR. Gynecologic consequences of bacterial vaginosis. *Obstet Gynecol Clin North Am.* 2003;(30):685-694.

5. Colli E, Landoni M, Parazzini F. Treatment of male partners and recurrence of bacterial vaginosis: a randomized trial. *Genitourin Med.* 1997;73:267-279.

6. Vejtorp M, Bollerup AC, Vejtorp L, et al. Bacterial vaginosis: a double-blind randomized trial of the effect of treatment of the sexual partner. *BJOG.* 1988;95:920-926.

7. Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal medications for gynecologic symptoms. *J Fam Pract.* 1996;42:595-600.

8. Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and clinical implications for therapy. *Clin Infect Dis.* 1999;28:S57-S65.

9. Schwebke JR, Desmond R. Risk factors for bacterial vaginosis in women at high risk for sexually transmitted diseases. *Sex Transm Dis.* 2005;32(11):654-658.

10. Genc MR, Witkin SS, Delaney ML, et al. A disproportionate increase in IL-1beta over IL-1ra in the cervicovaginal secretions of pregnant women with altered vaginal microflora correlates with preterm birth. *Am J Obstet Gynecol.* 2004;190(5):1191-1197.

11. Koumans EH, Kendrick JS, for the CDC Bacterial Vaginosis Working Group. Preventing adverse sequelae of bacterial vaginosis: a public health program and research agenda. *Sex Trans Dis.* 2001;28:292-297.

12. Gravett MG, Hummel D, Eschenbach DA, Holmes KK. Preterm labor associated with subclinical amniotic infection and with bacterial vaginosis. *Obstet Gynecol.* 1986;67:229-237.

13. Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of low-birth-weight infants. The Vaginal Infections and Prematurity Study Group. *N Engl J Med.* 1995;333:1737-1742.

14. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med.* 2000;342:1500-1507.

15. Larson PG, Platz-Christiansen JJ, Thejls H, et al. Incidence of pelvic inflammatory disease after first trimester legal abortion in women with BV after treatment with metronidazole: a double blind, randomized study. *Am J Obstet Gynecol.* 1992;166:100-101.

16. Nyirjesy P. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Vaginitis. *Clinical Management Guidelines for Obstetrician-Gynecologists.* May 2006;72:2-9.

17. Sobel JD. Bacterial vaginosis. *Ann Rev Med.* 2000;51:349-356.

18. Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. *N Engl J Med.* 2005;353:1899-1911.

19. O'Brien RF. Bacterial vaginosis: many questions—many answers? *Curr Opin Pediatr.* 2005;17(4):473-479.

20. Marazzo JM, Koutsky LA, Eschenbach DA, et al. Characterization of vaginal flora and bacterial vaginosis in women who have sex with women. *J Infect Dis.* 2002;185:1307-1313.

21. Barbone F, Austin H, Louv WC, et al. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis and bacterial vaginosis. *Am J Obstet Gynecol.* 1990;163:510-514.

22. Spiegel CA. Bacterial vaginosis. *Rev Med Microbiol.* 2002;13:43-51.

23. Van de Weijgert HJJM, Mason PR, Swanzura L et al. Intravaginal practices, vaginal floral disturbances and acquisition of sexually transmitted disease in Zimbabwean women. *J Infect Dis.* 2001;181:587-594.

24. Potter J. Should sexual partners of women with bacterial vaginosis receive treatment? *Br J Gen Pract.* 1999;49(448):913-918.

25. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines—2006. *MMWR.* August 4, 2006;55(RR-11):49-52. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5106a1.htm

26. Nansel TR, Riggs MA, Yu K-F, et al. The association of psychosocial stress and bacterial vaginosis in a longitudinal cohort. *Am J Obstet Gynecol.* 2006;194:381-386.

27. Joesoef M, Schmid G. Bacterial vaginosis. *Clin Evid.* 2003;(10):1824-1833.

28. Yudin MH, Landers DV, Meyn L et al. Clinical and cervical cytokine response to treatment with oral and vaginal metronidazole for bacterial vaginosis during pregnancy: a randomized trial. *Obstet Gynecol.* 2003;102:527-534.

29. Draper DL, Landers DV, Krohn MA, Hillier LS. Levels of vaginal secretory leukocyte protease inhibitor are decreased in women with reproductive tract infections. *Am J Obstet Gynecol.* 2000;183(5):1243-1248.

30. Secor RMC. Vaginal microscopy: refining the nurse practitioner's technique. *Clin Excell Nurse Pract.* 1997;1(1):29-34.

31. Davis JD, Connor EE, Clark P, et al. Correlation between cervical cytologic results and Gram stain as diagnostic tests for bacterial vaginosis. *Am J Obstet Gynecol.* 1997;177(3):532-535.

32. Sweet, RL, Gynecologic conditions and bacterial vaginosis: implications for the non-pregnant patient. *Infect Dis Obstet Gynecol.* 2000;8:184-190.

33. Hillier SL, Martius J, Krohn M, et al. A case–control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *N Engl J Med.* 1988;319:972-978.

34. Yudin MH. Bacterial vaginosis in pregnancy: diagnosis, screening, and management. *Clin Perinatol.* 2005; 32(3):617-627.

35. Ugwumadu A, Reid F, Hay P, Manyonda I. Natural history of bacterial vaginosis and intermediate flora in pregnancy and effect on oral clindamycin. *Obstet Gynecol.* 2004; 104(1):114-119.

36. Kiss H, Petricevic LJ, Husslein P. Prospective randomized controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ.* 2004;329:371-375.

37. McDonald H, Brocklehurst P, Parsons J, Vigneswaran R. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev.* 2003:CD000262.

38. US Preventive Services Task Force. Screening for bacterial vaginosis: recommendations and rationale. *Am J Prev Med.* 2001;20(3S):59-61.

39. Larsson PG, Fahraeus L, Carlsson B, et al. Late miscarriage and preterm birth after treatment with clindamycin: a randomized consent design study according to Zelen. *BJOG.* 2006;113(6):629-636.

40. Lamont RF, Duncan SL, Mandal D, Bassett P. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol.* 2003;101:516-522.

41. Hillier S. Treatment of recurrent bacterial vaginosis. *Clin Rev.* 2004; 14(6):97-106.

42. Cole DS. Highlights in gynecology. Presented at: American College of Obstetricians and Gynecologists (ACOG) 53rd Annual Clinical Meeting; May 7-11, 2005; San Francisco, Calif.

43. MetroGel-Vaginal Prescribing Information. Northridge, Calif: 3M Pharmaceuticals; 1997. Available at: http://multimedia.mmm.com/mws/mediawebserver.dyn?6666660Zjcf6lVs6EVs66Sy&9COrrrrQ-

44. Ferris DG, Litaker MS, Woodward L, et al. Treatment of bacterial vaginosis: A comparison of oral metronidazole, metronidazole vaginal gel and clindamycin vaginal cream. *J Fam Pract.* 1995;41(5):444-445.

45. Fischbach F, Peterson E, Weissenbacher ER, et al. Efficacy of clindamycin vaginal cream versus oral metronidazole in the treatment of bacterial vaginosis. *Obstet Gynecol.* 1993;82:407-408.

46. Schmitt C, Sobel JD, Meriwether C. Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. *Obstet Gynecol.* 1992;79(6):1020-1023.

47. Clindesse Prescribing Information. St Louis, Mo: Ther-Rx Corporation. Available at: http://www.clindesse.com/pdf/PI.pdf

48. Merabet J, Thompson D, Saul Levinson R. Advancing vaginal drug delivery. *Expert Opin Drug Deliv.* 2005;2(4):770-772.

49. Faro S, Skokos CK, for the Clindesse Investigators Group. The efficacy and safety of a single dose of Clindesse vaginal cream versus a seven-dose regimen of Cleocin vaginal cream in patients with bacterial vaginosis. *Infect Dis Obstet Gynecol.* 2005;13(3):157-159.

50. Cleocin HCl Prescribing Information. Pfizer; 2003. Available at: http://www.pfizer.com/pfizer/download/uspi_cleocin_hcl.pdf

51. Koumans EH, Markowitz LE, Hogan V, for the CDC Bacterial Vaginosis Working Group. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. *Clin Infect Dis.* 2002;35(suppl 2):S152-S172.

52. Boskey, ER. Alternative therapies for bacterial vaginosis: a literature review and acceptability survey. *Altern Ther Health Med.* 2005; 11(5):38-43.

53. Nyirjesy P, McIntosh MJ, Gattermeir DJ, et al. The effects of intravaginal clindamycin and metronidazole therapy on vaginal lactobacilli in patients with bacterial vaginosis. *Am J Obstet Gynecol.* 2006;194:1277-1282.

54. Beigi RH, Austin MN, Krohn MA, Hillier SL. Antimicrobial resistance associated with the treatment of bacterial vaginosis. *Am J Obstet Gynecol.* 2004;191:1124-1129.

55. Cleocin (Clindamycin Phosphate) Vaginal Cream Prescribing Information. Available at: www.fda.gov.medWatch/SAFETY/2003/03AUG_PI/Cleocin_PI.pdf

56. Wilson J. Managing recurrent bacterial vaginosis. *Sex Transm Infect.* 2004;80:8-11.

57. Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. *Am J Obstet Gynecol.* 2006; 194(5):1283-1289. Epub 2006 Apr 21.

58. Smart S, Singal A, Mindel A. Social and sexual risk factors for bacterial vaginosis. *Sex Transm Infect.* 2004;80:58-62.