CME

Bacterial vaginosis: A practical review

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ABSTRACT

Bacterial vaginosis is a common vaginal infection that causes discharge, odor, and irritation. It can predispose women to sexually transmitted infections (STIs) including HIV. Recurrent bacterial vaginosis may require prolonged treatment to return the vaginal flora to a normal predominately lactobacilli-dominated environment.

Keywords: bacterial vaginosis, *Gardnerella*, sexually transmitted infections, pelvic inflammatory disease, vaginitis, HIV

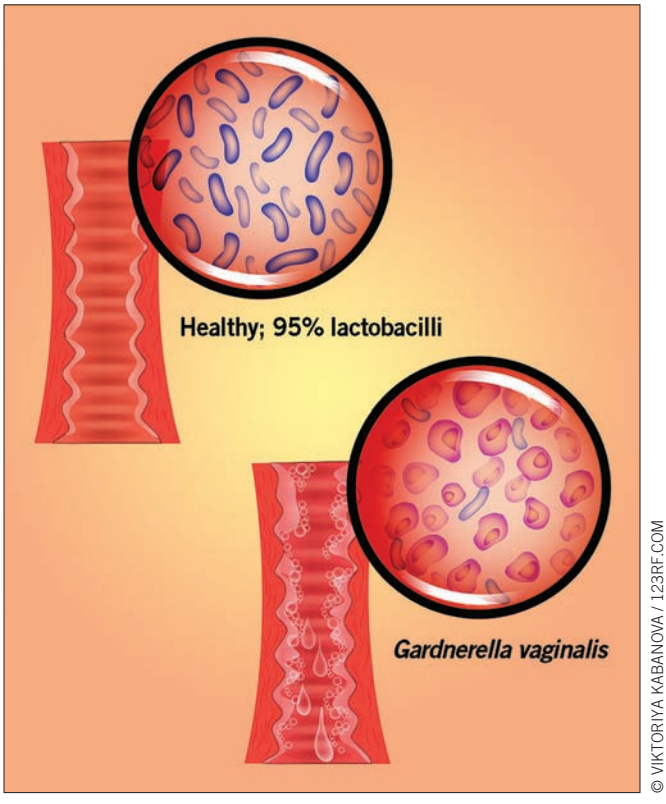
Learning objectives

- List the risk factors for bacterial vaginosis and how these should be addressed in the management strategy.
- Describe the various diagnostic strategies used to confirm the presence of the infectious causes of bacterial vaginosis.
- Devise an appropriate therapeutic regimen for the patient with newly diagnosed bacterial vaginosis or for recurrent infection.

Bacterial vaginosis, formally known as *Gardnerella* vaginitis, is a common dysbiosis affecting about 21 million women in the United States.[1,2] Bacterial vaginosis often recurs after treatment, with 50% of women having return of symptoms within 12 months.[3] Some research suggests that it may precipitate preterm labor and has been associated with the development of pelvic inflammatory disease (PID).[4,5] Bacterial vaginosis predisposes women to the acquisition of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV).[6,7] It affects black and Hispanic women disproportionately, puts them at risk for STIs and HIV, and may predispose them to preterm birth.[2]

EPIDEMIOLOGY AND RISK FACTORS

Bacterial vaginosis is the most common cause of vaginal discharge and odor in women, affecting 29% of women overall. Risk factors include:



- black or Hispanic ethnicity
- douching regularly
- smoking
- multiple sex partners
- not using condoms
- sex with women (usually both women are affected).[1-3,8]

Women who use a combined method of birth control, such as an oral contraceptive, have lower rates of bacterial vaginosis.[2,3] Oral estrogen in the pill is thought to have a nurturing effect on the lactobacilli in the vagina and may explain the lower rate of bacterial vaginosis in women who use oral contraceptives.[3]

PATHOPHYSIOLOGY

The cause of bacterial vaginosis is not known; however, it may be sexually assisted and sexually transmitted.[9] The theory of sexual transmission is supported by recovery of *Gardnerella vaginalis* from the urethra and penile skin of male partners of women with bacterial vaginosis.[10] Women with recurrent bacterial vaginosis often have the same partner before and after treatment, and may be reinfected

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Key points

- Bacterial vaginosis is a common vaginal infection and can predispose women to STIs including HIV.
- The condition recurs in 50% of women within 12 months, and may require prolonged treatment.
- Current treatments have been unable to produce a lasting cure in many women affected by recurrent bacterial vaginosis.
- Longer treatment with vaginal probiotics may further reduce recurrences following antibiotic treatment.

with *G. vaginalis* by their male partner.[10] The high rate of vaginal bacterial concordance in women who have sex with women further supports the assumption that bacterial vaginosis may be sexually transmitted.[11]

In women with bacterial vaginosis, the native vaginal flora—hydrogen-peroxide producing lactobacilli responsible for maintaining an acidic environment—are replaced with invasive pathogens, *G. vaginalis, Prevotella* species, and *Mobiluncus* species.[12] The replacement of lactobacilli with *G. vaginalis* promotes a basic pH that sets the environment for bacterial vaginosis. *G. vaginalis* produces a biofilm that provides a matrix for other pathogenic bacteria to cling to, as well as making it harder for antibiotic therapy to penetrate and eradicate the infection.[8,13]

HISTORY AND PHYSICAL EXAMINATION

Women typically present with complaints of vaginal discharge, odor, and sometimes irritation.[1] Patients may report a previous episode of bacterial vaginosis within the previous 3 months to 1 year, as the recurrence rate of bacterial vaginosis following treatment is about 50%.[2,5] Physical examination of the vagina typically demonstrates a thin milky discharge and at times a fishy odor is detectable.[1] The bimanual examination usually is normal.

DIAGNOSIS

Collection of vaginal discharge with a cotton tipped swab from the lateral and posterior vaginal walls is sufficient for pH measurement and wet mount microscopy. Applying the swab to pH paper will show an alkaline environment with a pH greater than 4.5.[1] A saline wet mount slide made from the vaginal secretions will show clue cells.[1] A 10% potassium hydroxide solution added to a slide of vaginal secretions will yield the fishy odor that is typical of bacterial vaginosis.[1] The differential diagnosis of bacterial vaginosis includes yeast and trichomonal vaginitis. Coinfection with *Chlamydia trachomatis* and *Neisseria gonorrhea* has to be considered as bacterial vaginosis makes it easier to acquire STIs. [6,12]

The gold standard for diagnosing bacterial vaginosis is through Gram staining and Nugent scoring.[14] This method involves identifying and quantifying lactobacilli as well as *G. vaginalis*, *Mobiluncus*, and *Bacteroides* species.[14] A numerical score is calculated by identifying how many lactobacilli or *G. vaginalis*, *Bacteroides*, or *Mobiluncus* are in each field on the microscope slide (**Table 1**). A score of 0-3 is deemed normal, 4-6 is considered intermediate, and 7-10 indicates bacterial vaginosis.[14] This method is not practical for most office settings as it requires an onsite laboratory and the expertise to identify different bacteria.[14]

Amsel criteria and Nugent scoring are considered equally efficacious in diagnosing bacterial vaginosis.[1,15] Meeting three of the four Amsel criteria is diagnostic for bacterial vaginosis:

- pH above 4.5 as measured with pH strips
- thin homogenous discharge
- fishy odor after application of 10% potassium solution to vaginal smear
- 20% or greater clue cells on saline microscopy.[1,15]

The wet mount microscopy also has the added benefit of identifying trichomonas and yeast budding and pseudohyphae. Clinicians can use Amsel criteria for office-based diagnosis and prompt initiation of treatment.[1,15]

TABLE 1. Nugent scoring for diagnosing bacterial vaginosis[14,50]

Lactobacilli are given a score of 0 if found in normal amounts and a numeric score if low in quantity or absent. The other organisms are scored based on numbers present. The sum of the three subscores is the patient's Nugent score: 0-3 is normal, 4-6 is intermediate, and 7-10 indicates bacterial vaginosis.

Number	Subscore
Number of lactobacillus Gram-positive rods	
≥30	0
5-20	1
1-4	2
<1	3
0	4
Number of *Gardnerella/Bacteroides* Gram-variable coccobacilli	
0	0
<1	1
1-4	2
5-30	3
≥30	4
Number of *Mobiluncus* curved Gram-negative bacilli	
0	0
<1	1
1-4	1
5-30	2
≥30	2

Alternate tests can be used to diagnose bacterial vaginosis if microscopy is unavailable. BV Blue detects sialidase activity and uses color change technology that is ready in 10 minutes. However, it does not detect trichomonas or candida species.[16] BV Blue costs about $17 per test and is covered by some health insurances.[16]

The Fem Exam test is a two-card system that detects pH and trimethylamine on one card and prolineaminopeptide (a chemical produced by *G. vaginalis*) on the other.[17] The test takes 5 minutes but does not detect trichomonas or *Candida* species.[17] The Fem Exam test costs more than wet mount microscopy ($8.32 to $18.49 per card) and is covered by some insurance plans.[17]

BD Affirm VPIII test for bacterial vaginosis uses DNA technology and can be ready in 45 minutes if there is a laboratory on site to process the specimen or if the practice owns the machine that analyzes the specimen.[18] BD Affirm VPIII test can identify bacterial vaginosis, along with trichomonas and *Candida*.[18] The BD Affirm VPIII analyzer system, test swabs, and reagents are costly but are covered by some insurance plans.[18]

The identification of vaginal flora consistent with bacterial vaginosis reported on a Pap smear cytology result is not considered diagnostic for bacterial vaginosis. The Pap smear has low sensitivity and specificity as a screening for bacterial vaginosis and should not be used to initiate treatment.[12,19]

The CDC recommends testing for *C. trachomatis*, *N. gonorrhea*, and *Trichomonas vaginalis* with the Aptima Gen-Probe when screening for women with bacterial vaginosis.[12] Vaginal symptoms can be caused by multiple pathogens and bacterial vaginosis places women at increased risk for acquiring STIs.[6,12] The CDC also recommends HIV testing be offered to any woman that is diagnosed with bacterial vaginosis as it is associated with an increased risk for acquiring HIV.[7,12]

TREATMENT GUIDELINES

The CDC's recommended treatment options for symptomatic women diagnosed with bacterial vaginosis are shown in **Table 2**.[12] Symptomatic pregnant women are treated the same as those who are not pregnant.[12,20]

Metronidazole is considered safe even in the first trimester and does not appear to contribute to low birth weight, premature birth, or birth defects.[20] Tinidazole has not been studied in pregnant women and should be avoided in this population.[12] Breastfeeding women can be treated safely with either oral or vaginal metronidazole.[21] Women who are HIV-positive receive the same treatment medications.[12] Advise patients to abstain from sex during treatment or use condoms.[12]

Adverse reactions to metronidazole are primarily gastrointestinal in nature, including nausea and vomiting. To avoid these adverse reactions, tell patients to take the medication with food.[5] A metallic taste while taking metronidazole is a common complaint.[5] Transient neutropenia and peripheral neuropathy have occurred in patients taking metronidazole but are uncommon.[5]

TABLE 2. CDC recommended treatments[12]

Choose one:

- Oral metronidazole 500 mg twice daily for 7 days
- 0.75% metronidazole gel, one applicator intravaginally every night for 5 nights
- 2% clindamycin vaginal cream, one applicator intravaginally every night for 7 nights

Alternate treatments (choose one):

- Oral tinidazole, 2 g/day for 2 days
- Oral tinidazole, 1 g/day for 5 days
- Oral clindamycin 300 mg twice daily for 7 days
- Clindamycin 100-mg ovules, intravaginally each night for 3 nights

Seizure activity has occurred rarely in patients taking metronidazole.[5] Metronidazole allergies are rare but if they occur they can present as rash, urticaria, or even anaphylaxis.[5] Tell patients to avoid alcohol while taking metronidazole because the combination causes a disulfiram-like reaction.[12] Metronidazole interacts with warfarin and certain anticonvulsants as well as lithium.[5] Metronidazole has been in use for around 24 years but thus far resistance has not been reported.[5]

Clindamycin is considered safe for use in pregnant women in both oral and vaginal forms.[12] Clindamycin vaginal cream is preferred for use in breastfeeding women over the oral formula as less is absorbed systemically.[21] The breastfeeding infant should be monitored for changes in stool such as diarrhea.[21] Oral clindamycin can cause nausea, vomiting, and abdominal pain.[22] Oral clindamycin has been associated with colonization with *Clostridium difficile* and pseudomembranous colitis.[22] Clindamycin vaginal cream has been associated with the development of yeast vaginitis. Clindamycin vaginal cream can weaken latex condoms and diaphragms; advise patients to use another method of birth control during treatment and for 5 days following treatment.[12]

Treatment of pregnant women with asymptomatic bacterial vaginosis is controversial. The US Preventive Services Task Force (USPSTF) recommends against screening for and treating asymptomatic bacterial vaginosis in women at low risk for preterm labor. The USPSTF concludes that in women at high risk for preterm birth, evidence is insufficient to recommend screening and treatment for asymptomatic bacterial vaginosis.[23]

Ugwumadu and colleagues conducted a randomized controlled trial screening women between 12 and 22 weeks of pregnancy for asymptomatic bacterial vaginosis and compared oral clindamycin 300 mg twice daily for 5 days with oral placebo.[24] The authors concluded that treating

asymptomatic bacterial vaginosis with oral clindamycin early in the second trimester reduced the rate of preterm birth by 10.4% and also reduced the rate of late miscarriage.[24]

Lamont and colleagues used a randomized double-blind, placebo-controlled trial that screened pregnant women between 13 and 20 weeks of pregnancy and randomized them to either a 3-day course of intravaginal 2% clindamycin cream or placebo cream.[25] The authors found a 60% reduction in preterm birth for the women treated with clindamycin vaginal cream compared with those using placebo.[25]

Joergensen and colleagues reviewed meta-analyses and systematic reviews that studied treatment of asymptomatic bacterial vaginosis in pregnant women to reduce risk of preterm birth.[26] The authors found that the existing meta-analyses and systematic reviews were heterogeneous and used antibiotics that were inappropriate as well as being used too late in pregnancy to stop preterm birth.[26] However, they concluded that using clindamycin before 22 weeks of pregnancy in women who had asymptomatic bacterial vaginosis reduced the rate of preterm birth and late miscarriage.[26]

> Recurrence rates of bacterial vaginosis remain high even after extended treatment.

Brocklehurst and colleagues conducted a systematic review of 21 studies and found no evidence to support routine screening and treatment of asymptomatic bacterial vaginosis in pregnant women, as it has not been shown to reduce the incidence of preterm birth.[27] The authors maintained that early screening of women who have recurrent bacterial vaginosis and effective treatment early in pregnancy or even before pregnancy may reduce the risk of preterm birth, but more studies are needed.[27]

PARTNER TREATMENT

Despite some literature that suggests that bacterial vaginosis may be sexually transmitted, the CDC does not recommend treatment for male partners of affected women.[12] A systematic review conducted by Mehta did not find male partner treatment to be helpful in preventing recurrent bacterial vaginosis.[28] However, Mehta found that the six randomized controlled trials were flawed, lacked appropriate treatment medications, and had poor randomization and incomplete follow-up, making results inconclusive.[28]

A study by Bukusi and colleagues using a topical microbicide applied to male partner's penis daily and before and after sex did not decrease the incidence of recurrent bacterial vaginosis and actually increased it.[29] The authors infer that residual bactericidal effect of the microbicide persisting on the penis may have affected flora in the vagina during sexual intercourse, which led to destruction of lactobacilli and overgrowth of bacterial vaginosis pathogens.[29] Clearly, more research is needed on treatment of male partners of women with recurrent bacterial vaginosis. However, treatment of female partners of women who have sex with women also should be considered as there is great concordance in their vaginal microbiomes.[11,30]

TREATING RECURRENT BACTERIAL VAGINOSIS

Half of women treated for bacterial vaginosis will experience a recurrence in the following 12 months.[3] Recommendations for treating a recurrence are not universal. The CDC recommends that infrequent recurrences can be managed using the same medications as an initial infection with bacterial vaginosis (**Table 2**).[12] Recurrent bacterial vaginosis after a second treatment with metronidazole or clindamycin should be managed more aggressively, particularly if the patient has monthly recurrences.[31]

Sobel and colleagues reported reduced recurrence using suppressive therapy with 0.75% metronidazole gel applied intravaginally twice weekly for 4 to 6 months; however, half the women experienced a relapse following cessation of therapy.[31]

Reichman and colleagues used oral metronidazole or tinidazole (500 mg twice daily for 7 days) followed by 21 days of intravaginal boric acid and maintenance therapy of 6 months of twice-weekly 0.75% metronidazole gel intravaginally.[32] This therapy resulted in an 87% cure rate at 28 weeks, followed by a 50% recurrence rate at 36 weeks.[32]

Aguin and colleagues studied using high-dose 750 mg metronidazole suppositories intravaginally for 7 nights, followed by 750-mg intravaginal suppositories twice weekly for 3 months.[33] Recurrences on this therapy were only 1% at 3 months, but after cessation of therapy, 50% of participants experienced a recurrence within 3 months.[33]

Krasnopolsky and colleagues treated women recently cured of bacterial vaginosis with metronidazole or clindamycin with 250 mg silicon-coated intravaginal vitamin C tablets, or an identically appearing placebo, for 6 days following each menstrual cycle for a total of 6 months or menstrual cycles.[34] This treatment halved the rate of recurrence of bacterial vaginosis compared with those using the intravaginal placebo.[34] The authors theorize that the acidification by intravaginal vitamin C inhibited pathogens that need a more basic pH and helped recolonize protective lactobacilli that need an acidic environment.[34]

Larsson and colleagues used clindamycin vaginal cream combined with oral clindamycin for 7 days followed by probiotic vaginal capsules for 5 days to treat recurrent

bacterial vaginosis.[35] Partner treatment with oral clindamycin also was used. Following the second menstrual cycle, the patient was treated with metronidazole vaginal for 5 days followed by another 5 days of vaginal lactobacilli capsules.[35] Following the third menstrual cycle, another round of metronidazole vaginal for 5 days was given. The cure rate at 6 months was 75%, but fell to 65% by 12 months and 56% by 24 months.[35]

Treatment of recurrent bacterial vaginosis can be difficult and may require extended courses of antibiotic therapy to obtain a long-lasting cure.[31] Treatment should be tailored to the patient and based on the frequency of the recurrences. Medications delivered vaginally, such as metronidazole gel, cause fewer systemic adverse reactions than oral medications and are preferred for maintenance therapy.[31] Yeast infections are common with extended treatment regimens and can be managed with oral fluconazole 150 mg.[31] Recurrence rates of bacterial vaginosis remain high even after extended regimens and research is being done to determine the most effective treatment.[31-33]

The persistent dysbiosis that characterizes recurrent bacterial vaginosis needs further study, and agents that can break down the biofilm produced by *G. vaginalis* may be necessary to eradicate the infection and produce a long-lasting cure.[8,32,34] Using probiotics to recolonize the vaginal flora following treatment may help promote a normal vaginal microbiome.[35]

NOVEL ANTIBACTERIAL TREATMENTS

A single-blind, randomized clinical trial by Weissenbacher and colleagues compared dequalinium chloride vaginal tablets used daily for 6 days with 2% clindamycin intravaginal cream used daily for 7 days. The results suggest that dequalinium chloride is as effective as clindamycin intravaginal cream. Lactobacilli recovery was superior in the dequalinium group compared with the clindamycin group.[36] Recurrence rates at 25 days post-treatment were reported as equal, although the authors do not quantify these further.[36]

Laghi and colleagues studied the use of rifaximin intravaginally with four different intervention arms.[37] Group A used rifaximin 100 mg vaginal tablets for 2 days and placebo vaginal tablets for 3 days, Group B used rifaximin 25 mg vaginal tablets for 5 days, Group C used rifaximin 100 mg vaginal tablets for 2 days followed by 3 days of vaginal placebo, and Group D used 5 days of vaginal placebo.[37]

Rifaximin restored lactobacilli and increased lactic acid in patients, with the Group B regimen producing the best results. However, the final patient visit was 28 days following treatment, so recurrence was not assessed.[37]

Zhong-Ming and colleagues compared sucrose gel applied intravaginally twice daily to metronidazole gel intravaginal once a day and found sucrose to be equally effective and promoted a more rapid restoration of normal flora.[38] No long-term follow-up was done to address the recurrence rate of bacterial vaginosis following sucrose gel treatment.[38]

PROBIOTIC THERAPY

Vujic and colleagues compared oral delivered probiotics, *L. rhamnosus* GR-1 and *L. reuteri* RC-14, two capsules a day for 6 weeks, with identical-looking placebo capsules. They found that after 6 weeks of treatment, 62% of women in the treatment group and 27% in the placebo group achieved a balanced vaginal microbiota.[39] At 12 weeks follow-up, the probiotic group had 50% normal microbiota compared with 20% of those in the placebo group.[39]

Ya and colleagues studied using vaginal probiotics *L. rhamnosus*, *L. acidophilus*, and *Streptococcus thermophiles* to prevent bacterial vaginosis recurrences.[40] Women were randomized to receive either vaginal probiotics or vaginal placebo for a treatment course of 7 days on, 7 days off, and 7 days on. The treatment group had a 16% recurrence rate compared with 45% in the placebo group at 2 months post-treatment. At 11 months post-treatment, 10.6% of women in the treatment group had a recurrence, compared with 27.7% in the placebo group.[40]

Bodean and colleagues studied the use of oral probiotics, vaginal probiotics, or no probiotics taken after metronidazole 500 mg twice daily for 7 days and metronidazole cream intravaginally for 5 days.[41] Group A received only the antibiotic therapy, Group B received the antibiotic therapy followed by vaginal probiotics for 6 days prepared with *L. rhamnosus B*, *L. acidophilus*, *S. thermophilis*, and *L. bulgaricus*. Group C received antibiotic therapy that was supplemented with oral probiotics containing *L. acidophilus*, *L. bifidus*, taken 2 hours after ingestion of the antibiotic for a total of 10 days.[41] All three groups were given therapy for four cycles: the initial treatment, and the identical treatment following three consecutive menstrual cycles.

At 3 months, Group A (no probiotics) had a 50% recurrence rate, Group B (vaginal probiotics) had a 30% recurrence rate, and Group C (oral probiotics) had a 15% recurrence rate.[41] The authors admitted to a lower rate of follow-up with the vaginal probiotic arm, possibly due to the vaginal route of administration being less acceptable to participants.[41] They proposed that probiotics can help to re-establish the lactobacilli in the vagina and help prevent recurrence of bacterial vaginosis.[41]

Marcone and colleagues studied the effect of vaginal probiotic *L. rhamnosus* applied intravaginally once weekly following metronidazole 500 mg orally twice daily for 7 days and continued for 2 months, versus no probiotic therapy.[42] The authors reported significantly less recurrence of bacterial vaginosis among those treated with the intravaginal probiotic, an effect that persisted for 6 months.[42]

They concluded that longer treatment with vaginal probiotics may further reduce recurrences following antibiotic treatment.[42]

COMPLICATIONS

Bacterial vaginosis can have a devastating effect on women, putting them at risk for STIs including HIV.[6,7] Bacterial vaginosis also may contribute to preterm birth and late miscarriage in pregnant women along with facilitating other gynecologic infections.[4,5,43]

A recent meta-analysis found a positive association between bacterial vaginosis and cervical human papillomavirus (HPV) infection.[44] Another study found *G. vaginalis* was recovered at a higher frequency in HPV-positive women.[45] This potential relationship between bacterial vaginosis and HPV deserves further investigation to delineate if having bacterial vaginosis puts women at greater risk for HPV and possible development of cervical dysplasia.[45]

Recurrent bacterial vaginosis can cause psychologic distress as women feel shame about the odor and avoid sexual relations.[46] Many women feel that they have no control over preventing recurrences and are concerned that the lingering infection may be harming them.[46] They dislike what they view as toxic treatments and want more options.[3,46] Women with recurrent bacterial vaginosis have a low level of satisfaction with their clinical management and feel that clinicians are not knowledgeable about the condition.[46]

LIFESTYLE CHANGES

Instructing women to stop douching can help reduce the recurrence of bacterial vaginosis.[47] Smoking cessation may help to reduce recurrences and should be recommended.[48] Limiting the number of sexual partners and consistent condom use can decrease recurrence as well.[3,49]

In patients using contraception, combined oral contraceptives can help reduce recurrence of bacterial vaginosis.[3] Because IUD use has been associated with a higher risk of infection, women who are considering an IUD and have a history of recurrent bacterial vaginosis may want to use an alternative method of contraception.[2,3] Changing bathing practices or wearing certain underwear material has not reduced rates of recurrent bacterial vaginosis.[47] Menstrual hygiene practices, such as using pads instead of tampons, also has not affected the incidence of recurrent bacterial vaginosis.[47,49]

AREAS FOR FURTHER STUDY

The possibility of sexual transmission as a mechanism for recurrent bacterial vaginosis should be further studied with well-designed randomized controlled trials of male partner treatment. Carefully designed studies also are needed to address whether early screening and treatment for bacterial vaginosis in asymptomatic pregnant women reduces the rate of preterm birth.

CONCLUSION

Bacterial vaginosis is a common vaginal dysbiosis that recurs in up to 50% of women treated with traditional therapy.[3] The same medications have been used for many years and have been unable to produce a lasting cure in many women affected by recurrent bacterial vaginosis.[5] Women need effective, long-lasting treatments because recurrent bacterial vaginosis can have a devastating effect on their health and feelings of well-being.[46] The unacceptably high recurrence rates of bacterial vaginosis highlight the need for new approaches to treatment. **JAAPA**

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