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WOMEN'S HEALTH UPDATE

Focus on Bacterial Vaginosis, Prenatal Nutrition, and Anemia

Recent advances in health care for women emphasize the importance of educating physicians and health care professionals in primary care about common conditions and needs of women of childbearing age, such as bacterial vaginosis, prenatal nutrition, and anemia.

Bacterial vaginosis is the most common cause of vaginitis in women of childbearing age, representing up to 50% of all cases. Recent research shows that prenatal nutrition should focus on combined dietary and supplemental therapies to improve the health of fetuses, neonates, and ultimately children and adults. Another common condition in women of childbearing age, anemia occurs gradually and is accompanied by insidious symptoms that vary significantly among patients, complicating diagnosis and often delaying treatment.

This monograph aims to deliver important information to obstetricians, gynecologists, family practice physicians, internists, nurse practitioners, physician assistants, and other providers in primary care. Enhanced with illustrative charts, figures, and graphs, the evidence-based text aims to educate clinicians about prevalence, screening, diagnosis, treatment, and counseling for each condition.

We hope you find the updated women's health information helpful to your clinical practice and an asset in improving health care outcomes in your patients.

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Advances in the diagnosis and treatment of bacterial vaginosis

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When a condition as common as bacterial vaginosis (BV) is suspected, patients and providers may be tempted to make a symptom-based diagnosis. Unfortunately, studies have shown the inaccuracy of such an approach. To avoid mistaking the cause of vaginal symptoms, in-office diagnosis according to standard criteria is recommended. A variety of formulations, dosing schedules, and antibiotics are available to meet the requirements of symptomatic women or women who require treatment prior to surgery, during pregnancy, or because of additional risk factors.

Bacteriology of BV

Bacterial vaginosis has a complex bacteriology, involving anaerobes and facultative anaerobes. The concentrations of bacteria increase 100-fold to 1000-fold in women with BV.[1] The organisms most commonly present are facultative anaerobes such as *Gardnerella vaginalis* and *Mycoplasma hominis*, and the anaerobic species *Prevotella* (formerly *Bacteroides*), *Peptostreptococcus*, *Eubacterium*, and *Mobiluncus*, and *Atopobium vaginae*. Frequently, the hydrogen peroxide–producing lactobacilli, which normally are part of the body's protective flora, are absent or greatly reduced in women with BV (**FIGURE 1**).[2]

A study by Fredricks and colleagues highlighted how much is yet to be learned about the diversity and complexity of the bacteria associated with BV.[3] The researchers evaluated the vaginal fluid of 27 women with BV and 46 without BV. They found that women infected with BV had a mean of 12.6 bacterial phylotypes. Women in the control group had a mean of 3.3 species, predominately lactobacillus species. The researchers also detected 3 new bacteria, related to bacteria in the *Clostridium* genus, only in women with BV.

KEY POINTS

- The defining characteristic of bacterial vaginosis (BV) is the replacement of normal vaginal lactobacillus bacterial flora with anaerobes and facultative anaerobes.
- A diagnosis of BV requires 3 of 4 Amsel's criteria. Standard treatment consists of an oral or topical antibiotic agent, usually clindamycin or metronidazole.

Who is at risk?

Bacterial vaginosis is the most common cause of abnormal vaginal discharge in women of reproductive age worldwide.[4] A national survey of almost 2000 women in the United States in 2001 and 2002 found that 27.4% had BV.[5] Risk factors associated with BV include recent antibiotic usage, smoking, numerous sexual partners, and routine douching.[6]

Although having a greater number of sexual partners has been associated with a greater risk of developing BV,[4] researchers still debate whether BV is sexually transmitted. Infection can occur if infected vaginal fluid is transferred between women,[7] which suggests BV can be transmitted sexually[8]; however, researchers in a study that included 91 women attending a specialist genitourinary medicine service for lesbians concluded that BV probably was not transmitted sexually.[9]

Condoms can decrease the risk of developing BV,[10] although studies show that treating sexual partners does not decrease recurrence of BV[11] and BV organisms have not been cultured from male partners.[12] In one study, the incidence of BV among women who were not sexually experienced was higher than anticipated based on previous epidemiologic studies, but this finding was likely due to use of highly sensitive criteria to diagnose BV.[13]

Diagnosis: Optimizing accuracy

At least 50% of women with bacterial vaginosis are completely asymptomatic.[14] Symptomatic patients may

complain of malodor, abnormal discharge, and, less commonly, vaginal/vulvar itching and irritation (approximately 10% of patients),[17] which may be mistaken for candidiasis.

Avoid diagnostic shortcuts

Women often find it expedient and convenient to self-diagnose and self-treat when they have vaginal symptoms. One study suggested that fairly accurate self-diagnosis could reduce annual direct health care costs by $45 million and create $19 million in indirect savings.[18] Unfortunately, self-diagnosis is rarely accurate.

When Ferris and colleagues quizzed 552 patients regarding hypothetical cases of vaginitis, only 28% could accurately diagnose vulvovaginal candidiasis (VVC) and only 4% recognized BV.[17] Diagnostic accuracy was no better among women who had previously had a yeast infection than among women who had not. Women without previous infections were, however, much more likely to say that they would diagnose and treat themselves if they thought they had VVC.

Unsurprisingly, inaccurate self-diagnosis of a yeast infection leads to inappropriate treatment with over-the-counter preparations. In a 2-year, prospective 5-center study, Ferris and colleagues offered 95 women who intended to use commercially available antifungal agents for their vaginal symptoms a free medical evaluation within 24 hours.[18] Actual diagnosis revealed that a wide range of conditions caused the women's symptoms and that self-treatment with antifungals would have been inappropriate or insufficient for 63 (66%) of the women in the study—all of whom believed they had a yeast infection.[18]

Health care providers may wish to offer women telephone consultations as an alternative to self-diagnosis, but a study of 253 patients who called the Kaiser Permanente Phone Call Center has shown that this approach to symptom assessment should be discouraged.[19] Callers were evaluated by a nurse over the phone and again by a clinician in the office. There was poor agreement between nurses and clinicians for a diagnosis of BV, VVC, or trichomoniasis, as well as between nurses and clinicians regarding the necessity of an office visit.

Use current standard for proper diagnosis

The current standard for clinical diagnosis of vaginal infections requires the presence of 3 of 4 Amsel's criteria:

- abnormal gray discharge
- vaginal pH higher than 4.5

FIGURE 1

Normal Flora

Lactobacilli

Gardenerella vaginalis
Genital mycoplasmata
Anaerobes
Mobiluncus species
Others

Normal vaginal flora is largely composed of lactobacilli with small numbers of other species, whereas anaerobes and a variety of other species predominate in the vaginas of women with bacterial vaginosis.

- a positive amine (whiff) test
- more than 20% of the epithelial cells are clue cells

Microscopy tests for the criteria include a saline (wet) mount to reveal clue cells and trichomonads and a 10% potassium hydroxide smear for hyphae or blastospores.[20]

Amsel's criteria are easy to use, do not require reagents, and produce rapid and relatively sensitive (92%) results.

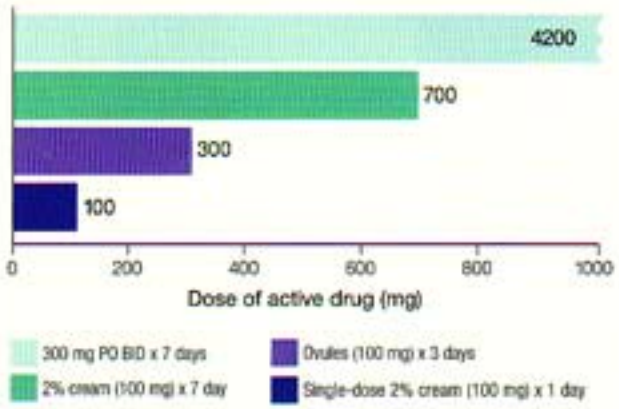
Data suggest that standards for diagnosis are not always followed. A retrospective review of records from 52 women referred to a tertiary-care vaginitis center for evaluation revealed that whiff and vaginal pH measurements were rarely (3%) performed by referring providers and that 42% of physicians did not perform a microscopy evaluation. In 54% of visits in which medication was prescribed, patients had an inadequate evaluation.[21]

Diagnostic test kits for BV

Several test kits are commercially available to help diagnose BV in the office. The QuickVue Advance® pH and Amine Test by Quidel Corporation (San Diego, Calif) is a card system to detect an abnormally elevated pH and high levels of amines (equivalent to a whiff test). The QuickVue Advance® *G vaginalis* test (for praline iminopeptidase activity) by Quidel Corporation and BVblue® (for vaginal sialidase) by Genzmye Corporation (Cambridge, Mass) measure high levels of proteins that are byproducts of the bacteria associated with BV. Exactly where these test kits fit into diagnostic algorithms remains to be determined and may depend on local factors such as availability of a microscope, Clinical Laboratory Improvement Amendments (CLIA) regulations, and cost versus reimbursement issues.

FIGURE 2

Total Dose of Active Drug per Treatment Regimen of Clindamycin



The total dose of clindamycin that constitutes a course of bacterial vaginosis treatment ranges from a low of 100 mg in a single-treatment vaginal product up to 4200 mg PO over 7 days.

Single-dose treatment: A new option

The US Food and Drug Administration recently approved a 2% clindamycin vaginal cream given as a single 100-mg dose for the treatment of BV, a regimen that has been included in recent ACOG guidelines.[20] The vehicle of the cream, a bioadhesive, biphasic system with a drug-laden internal phase and a water-soluble external phase, results in less product leakage than a standard cream.[22] Because it also permits slow release of clindamycin into the vagina, single-dose clindamycin vaginal cream treats BV with 100 mg of clindamycin instead of the 700-mg total dose in a 7-day cream (**FIGURE 2**).[23]

A multicenter, randomized, parallel-group study of 253 patients with BV compared the efficacy of single-dose clindamycin vaginal cream to treatment with a standard regimen of 7 nightly clindamycin vaginal cream doses.[24] The clinical cure rates (defined here as resolution of 3 of 4 Amsel's criteria) were similar between treatments: 87.5% with the single dose and 83.2% with the multiple-dose cream (**FIGURE 3**).

Goals of treatment

The goal of BV treatment is to promote a predominance of lactobacilli in a woman's vaginal flora and to decrease anaerobic and other bacteria. There are no effective means to administer lactobacilli, particularly those that produce hydrogen peroxide. Despite common belief, eating or douching with yogurt is not curative. *Lactobacillus acidophilus*, the bacteria contained in the most commonly used lactobacilli supplements, usually does not make hydrogen peroxide. Current BV treatment therefore depends on natural regeneration of lactobacilli while antibiotics target pathogenic bacteria.

CDC treatment guidelines

The Centers for Disease Control and Prevention (CDC) 2006 Sexually Transmitted Diseases Treatment Guidelines recommend the following treatments for BV[5]:

- Oral metronidazole, 500 mg, twice daily for 7 days *or*
- Metronidazole gel, 0.75%, 1 full applicator (5 g) intravaginally, once daily for 5 days *or*
- Clindamycin cream, 2%, 1 full applicator (5 g) intravaginally at bedtime for 7 days

As alternative regimens, the CDC guidelines recommend oral clindamycin, 300 mg, twice daily for 7 days or clindamycin ovules, 100 mg, intravaginally once at bedtime for 3 days.

Selecting a therapy for BV: Route of administration and antibiotics

Health care providers and patients have options when selecting a formulation and an antibiotic for BV. With equivalent efficacy among available treatments, the choice of one may depend on factors such as cost, convenience, compliance, and patient preference (**TABLE**).

Oral vs topical therapy

Oral therapy is less messy and expensive than topical therapy, it can be taken anywhere, and has no local side effects. However, oral therapy with metronidazole or clindamycin may have gastrointestinal side effects that in some cases can be severe and may include a metallic taste, nausea, vomiting, and diarrhea. Oral therapy also may interact with other medications; for example, metronidazole will increase levels of warfarin and lithium.

During treatment with vaginal creams, patients should be instructed not to engage in vaginal intercourse or use other vaginal products (eg, tampons or douches). In addition, cream formulations contain mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, patients should not use such barrier contraceptives concurrently or for 5 days after treatment with topical vaginal treatments, as they may not be reliable for preventing pregnancy or for protecting against transmission of human immunodeficiency virus (HIV) and other sexually transmitted infections.

Metronidazole vs clindamycin

Alcohol ingestion is discouraged while taking metronidazole, because of a possible disulfiram-like reaction. There are no restrictions on alcohol for women who take clindamycin.

Clindamycin has shown better efficacy than metronidazole against *Mobiluncus* species, whose presence on Gram stain may be a marker for a more severe BV infection.[23] In vitro susceptibility testing was performed on 159 BV-associated anaerobic isolates from pregnant Japanese and Thai women with an array of antibiotics, including clindamycin and metronidazole. Clindamycin was active against all isolates, whereas metronidazole was active against almost all isolates except *Mobiluncus* species.

In a recent randomized clinical study, anaerobic bacteria obtained from women with BV demonstrated an increasing resistance to clindamycin. Vaginal metronidazole or clindamycin ovules were used for 3 days by 95 women, and anaerobic isolates underwent microbial testing.[26] Of 1059 isolates, less than 1% were resistant to metronidazole, but 16% demonstrated resistance to clindamycin at baseline and 59% after therapy. These microbiologic findings highlight differences between clindamycin and metronidazole preparations, but their clinical relevance to patient outcome remains unclear and clinical cure rates seem to be similar between patients treated with both antibiotics.

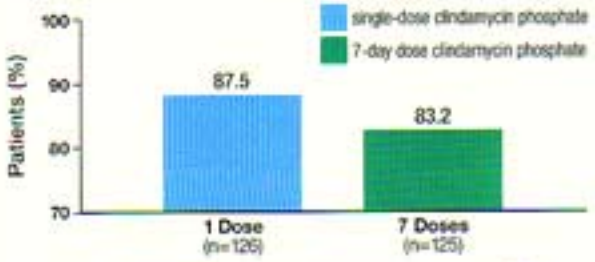
Clindamycin's spectrum of activity includes lactobacilli; however, its effect appears to be transient. In a retrospective analysis that compared data from 3 similarly designed studies that had evaluated single-dose 2% clindamycin vaginal cream, multiple-dose 2% clindamycin vaginal cream, and multiple-dose 0.75% metronidazole gel in women with BV, all groups exhibited a similar rise in lactobacilli on Gram stain 30 days after treatment.[27]

Individualizing treatment for special populations

Patients with recurrent infection. Recurrence is common with BV. Short-term failure, defined as a recurrence within 1 month after therapy, may be as high as 20% to 40% depending on the study. This type of failure presumably occurs because of persistent pathogenic flora. The exact incidence of long-term treatment failures occurring 3 to 6 months after therapy is unknown but is thought to be 30% or higher, most likely because of the failure to reestablish lactobacilli. In a prospective randomized trial, 157 patients with recurrent BV—an average of 5.1 BV episodes in the prior year—received a 10-day treatment course with nightly metronidazole; 88% of the patients were cured immediately after treatment.[28] Those cured were randomized to twice-weekly maintenance therapy with metronidazole cream or placebo for 4 months. At the end of the treatment period, 70% of those who had the active ingredient (metronidazole gel) were free of BV versus 34% in the placebo group.

FIGURE 3

Clinical Cure Rates With Clindamycin Vaginal Cream



Clinical cure rates were similar between single-dose and 7-day clindamycin vaginal creams for bacterial vaginosis.

Faro S, et al. *Infect Dis Obstet Gynecol.* 2005;13:155-160.

Asymptomatic patients. Women with BV who are undergoing a hysterectomy or abortion benefit from treatment for the infection, even if they are asymptomatic. Treated women experience less endometritis or cuff cellulitis after their procedure than women whose BV remains untreated.[4]

There is no general recommendation for treating asymptomatic women who are not undergoing surgery. However, some researchers recommend treating BV in patients at high risk for HIV infection, because of its association with increased HIV acquisition and other comorbidities.[4]

Pregnant women. Compelling multinational epidemiologic studies show an association between BV and a variety of poor pregnancy outcomes, such as prematurity, ruptured membranes, infection, and postpartum endometritis. Symptomatic pregnant women in any trimester should therefore be treated for BV. Oral metronidazole, either 500 mg twice daily or 250 mg 3 times daily for 7 days, or oral clindamycin, 300 mg twice daily for 7 days, is recommended by the CDC.[4]

There is no CDC recommendation on screening or treating pregnant women with asymptomatic BV. However, 3 of 4 prospective trials have shown benefit in women with asymptomatic BV who had a previous

TABLE

Choosing the Correct Therapy for Each Patient

Factor	Oral Metronidazole	Vaginal Metronidazole	Clindamycin Phosphate Vaginal Ovules	Vaginal Clindamycin Phosphate 2% Cream
Cost	Yes	No	Equivocal	No
Convenience	Yes	No	No	Yes
Compliance	No	No	No	Yes
Efficacy	Yes	Yes	Yes	Yes
Spectrum	Equivocal	Equivocal	Equivocal	Equivocal
Preference	?	?	?	?

yes=an advantage; no=a disadvantage; ?=unknown.

poor pregnancy outcome.[6] One study of BV treatment with oral clindamycin in early pregnancy (<20 weeks) showed a decrease in preterm birth.[29]

Summary

Bacterial vaginosis is a common condition that is frequently ignored and misdiagnosed. Properly performed standard office testing can lead to a correct diagnosis. For symptomatic women with BV, multiple treatment options are available that permit individualized therapy. Although asymptomatic women often are not treated for BV, surgical patients, pregnant women, and women at high risk of HIV infection may benefit from BV treatment, even in the absence of symptoms. Whether and when to screen and treat low-risk pregnant women with asymptomatic BV is still being actively debated. New data support specific strategies, such as maintenance regimens, to treat women with frequent recurrences. ■

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