

Bacterial Vaginosis: Review of Treatment Options and Potential Clinical Indications for Therapy

M. R. Joesoef, G. P. Schmid, and S. L. Hillier

From the Division of STD Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; and the Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

We reviewed data on the treatment of bacterial vaginosis published from 1993 through 1996. For nonpregnant women, we recommend use of metronidazole (500 mg orally twice daily for 7 days), clindamycin vaginal cream (2%, once daily for 7 days), or metronidazole vaginal gel (0.75%, twice daily for 5 days) as the preferred treatment for bacterial vaginosis. For pregnant high-risk women (women with a prior preterm birth), the objective of the treatment is to prevent adverse outcomes of pregnancy, in addition to relief of symptoms. Thus, systemic therapy for possible subclinical upper tract infection as well as medication that has been studied in pregnant women are preferable. Therefore, we recommend metronidazole (250 mg orally three times a day for 7 days). For pregnant low-risk women (women without a prior preterm birth) with symptomatic diseases, the main objective of the treatment is to relieve symptoms. We recommend metronidazole (250 mg orally three times a day for 7 days). Data do not support routine treatment of male sex partners.

Bacterial vaginosis (BV), the most prevalent infectious cause of vaginitis [1], is an imbalance of the bacterial vaginal flora. While some women with BV have symptoms such as an excess vaginal discharge or an odor, especially after sexual intercourse or menses, half have no symptoms [2]. In women with BV, the normal vaginal flora is altered from a predominance of H₂O₂-producing *Lactobacillus* species to high concentrations of anaerobic bacteria (e.g., *Prevotella*, *Bacteroides*, or *Mobiluncus* species), *Gardnerella vaginalis*, and *Mycoplasma hominis* [3]. The cause of this alteration is not fully understood, but the incidence of BV is increased among women who have multiple sex partners [4–6], use an intrauterine device for contraception [5], douche routinely for hygiene [6], or lack H₂O₂-producing strains of lactobacilli in the vagina [6]. Because of the polymicrobial nature of this condition, the treatment, cure, and management of recurrences are more complex than for many diseases caused by a single infectious agent.

Since our previous publication in 1995 [7], several reports of clinical trials of treatment for BV (especially of treatment during pregnancy and the use of intravaginal regimens) have been published. In this article, we briefly review the diagnosis of BV and then focus on its treatment with oral and intravaginal regimens (of clindamycin vaginal cream and metronidazole gel), highlighting the treatment of BV among pregnant women. The primary objective of BV treatment in nonpregnant women is to alleviate symptoms, while additional goals of therapy for

pregnant women are to limit exposure to medication and prevent adverse outcomes of pregnancy. Therefore, we recommend different treatment regimens for nonpregnant and pregnant women and review the controversial issue of screening for and treatment of BV in pregnant women. Last, we address the issue of whether sex partners of women with BV should be treated, as well as the screening and treatment of women about to undergo gynecologic surgery.

Methods

To update information on the treatment of BV, we reviewed articles published from 1993 through 1996. For the literature search, we used MEDLINE (and the terms *bacterial vaginosis*, *nonspecific vaginosis*, *clindamycin*, and *metronidazole*), textbooks about sexually transmitted diseases, abstracts from meetings of professional associations (e.g., the Infectious Diseases Society of America and the International Society of Sexually Transmitted Diseases Research), and information from drug manufacturers. For each study, we assessed study design (e.g., a randomized controlled trial or a case series), study population, treatment, outcome measures, reported findings, and potential biases in the study design and analysis. To examine issues other than treatment of BV, which required the use of data published earlier than 1993 to produce an accurate and balanced review, we also included older literature identified through the same methods.

Diagnosis of BV

Clinical diagnosis. Most investigators used a clinical definition for BV that was based on the composite criteria proposed by Amsel et al. [8], who required three of the following four

Reprints or correspondence: Dr. M. R. Joesoef, Division of STD Prevention, Mailstop E02, Centers for Disease Control and Prevention, Atlanta, Georgia 30333.

signs: (1) the presence of clue cells; (2) a homogeneous discharge that adheres to the vaginal walls; (3) pH of vaginal fluid of >4.5 ; and (4) a "fishy," amine odor of the vaginal discharge before or after addition of 10% KOH (the "whiff" test). Because commonly used pH paper does not have the color for a pH of 4.6, most clinicians use the pH color for 4.7 or greater as a diagnostic criterion for BV.

Gram stain diagnosis. The use of gram staining of vaginal fluid to diagnose BV was introduced by Dunkelberg in 1965 [9]. The method used the presence of *G. vaginalis* (small gram-negative bacilli) as the only criterion for the diagnosis of BV. In 1983 Spiegel et al. [10] introduced a gram-stained-smear method to diagnose BV that quantified microbial morphotypes into four categories: 1+ (<1 per field), 2+ (1–5 per field), 3+ (6–30 per field), and 4+ (>30 per field). The smear is interpreted as consistent with BV if the *Lactobacillus* morphotype (large gram-positive rod) is diminished (1+ or 2+) and other morphotypes (*Gardnerella* and anaerobes) are increased (3+ or 4+).

In 1990 Nugent et al. [11] introduced a standardized scoring system for the gram stains. In this scoring system, three morphotypes are used to create a total score of 0–10. These morphotypes are large, gram-positive rods (*Lactobacillus* species), small gram-negative or gram-variable rods (*Bacteroides* or *Gardnerella* species), and curved gram-negative to gram-variable rods (*Mobiluncus* species). The total score is the sum of the weighted quantity (0, 1–4+) of the three morphotypes. A score of 7–10 is considered diagnostic of BV. This scoring system increases the reliability of the interpretation of the gram stain [11, 12].

In general, gram stain-based diagnosis correlates well with clinical diagnosis and is an accepted diagnostic method. The gram stain is also less subjective than any of the clinical criteria other than pH. In a recent multicenter study comparing gram-staining of vaginal smears to the standard criteria of Amsel et al. [8] for diagnosis of BV, the sensitivity of the gram stain method was 89% and the specificity was 83% [13]. That the methods are relatively agreeable is important, as the diagnostic criteria that are used from study to study are quite diverse and, unfortunately, often do not adhere strictly to published criteria.

Treatment

Treatment of BV with Oral Metronidazole and Intravaginal Formulations

As in 1993, we still recommend the 7-day regimen of oral metronidazole for the treatment of BV, but application of the intravaginal products—clindamycin vaginal cream and metronidazole gel—has proved to be as efficacious as the 7-day oral regimen. Since 1993, no further investigators have reported on the use of a single 2-g dose of metronidazole. Larsson [14] in 1992 computed for double-blind studies (with no placebo comparison) a higher cumulative cure rate with the 7-day met-

ronidazole regimen than with the single-dose regimen (88% vs. 54%). In our previous review in 1993 [7], we concluded that the 7-day regimen of metronidazole (500 mg twice daily for 7 days) was more efficacious than the single-dose regimen of 2 g of metronidazole (cumulative cure rates 3–4 weeks after completion of treatment, 82% vs. 62%). On the basis of this 1993 review, we recommended a 7-day regimen for the treatment of BV.

Clindamycin is active against most organisms associated with BV, including *G. vaginalis* and *Mobiluncus* species, with respective MIC ranges of 0.06–0.125 $\mu\text{g/mL}$ and 0.06–0.25 $\mu\text{g/mL}$ [15, 16]. The cumulative cure rate for clindamycin 2% vaginal cream (5 g at bedtime for 7 consecutive days) 4–10 days after completion of treatment is 80%, and the cumulative cure rate 25–39 days after completion of treatment is 82% (table 1) [17, 18]. Similarly, for treatment with metronidazole vaginal gel 0.75% (5 g twice a day for 5 days), the cumulative cure rate 4–16 days after treatment completion is 81%, and the cumulative cure rate 28–32 days after treatment completion is 71% (table 2) [19, 20]. The differences in cumulative cure rates with the clindamycin cream and metronidazole gel are not statistically significant.

Comparing studies of regimens of oral metronidazole (500 mg twice a day for 7 days), clindamycin vaginal cream (5 g at bedtime for 7 consecutive days), and metronidazole vaginal gel (5 g twice a day for 5 days), we found that the cumulative cure rates 5–10 days after completion of treatment are 86% for the oral metronidazole, 85% for clindamycin vaginal cream, and 81% for metronidazole vaginal gel (table 3) [21–26]. The cumulative cure rates 4 weeks after treatment completion are 78% for oral metronidazole, 82% for clindamycin vaginal cream, and 71% for metronidazole vaginal gel (table 3) [21–26]. The differences in cumulative cure rates among the regimens of oral metronidazole, clindamycin vaginal cream, and metronidazole gel are not statistically significant. Thus, we recommend that a regimen of clindamycin cream 2% (5 g at bedtime for 7 consecutive days) or metronidazole gel 0.75% (5 g twice a day for 5 days) be considered as effective as a 7-day oral regimen of metronidazole.

It is possible that metronidazole vaginal gel, used in published studies only as a twice-a-day application, may be effective if used once a day, as is clindamycin cream. A study comparing metronidazole vaginal gel 0.75%, used once vs. twice daily for 5 days, found similar efficacy (3M Pharmaceuticals, St. Paul; data on file). With publication of the study of a daily metronidazole gel regimen and perhaps with further experience with this regimen, its use may be recommended in the future.

Treatment with Oral Regimens Other Than Metronidazole

Since our last review, no further randomized controlled trials have been done on the use of oral clindamycin as therapy for BV. Thus, the only trial of oral clindamycin at a dosage of

Table 1. Summary of data from studies of bacterial vaginosis in nonpregnant symptomatic women, in which a treatment regimen of clindamycin vaginal cream 2%, 5 g at bedtime for 7 days, was compared with placebo.

Reference	Study design, n	Inclusion criteria	Cure definition	Follow-up visits*	Treatment regimen	Cure rate: % (no.) cured
[17]	RDB, 32	CC plus ≥ 2 of the following: HD, pH of >4.5 , and AO	Absence of CC plus absence of ≥ 2 of the following: HD, pH of >4.5 , and AO	4–7 d	Clindamycin	94 (16)
				4–5 w	Placebo	25 (16)
[18]	RDB, 215	CC, pH of >4.5 , AO, and GS(N)	Absence of ≥ 2 of the following: pH of >4.5 , CC, and AO	5–10 d	Clindamycin	77 (65)
				25–39 d	Placebo	25 (69)
					Clindamycin	79 (57)
					Placebo	35 (51)
Summary				4–10 d	Clindamycin	80 (81)
				25–39 d		82 (73)

NOTE. AO = amine odor; CC = clue cells; GS(N) = positive gram stain (by Nugent’s method); HD = homogeneous discharge; NA = data not available; RDB = randomized double-blind controlled trial.

* After completion of treatment.

300 mg twice daily for 7 days remains that of Greaves et al. [27], in which the clinical response to clindamycin (94%) and metronidazole (500 mg twice a day for 7 days; 96%) was similar. We believe further study of the oral clindamycin regimen must be done before it can be considered to have efficacy equal to those of the recommended regimens, as we discussed in our last review [7]. Thus, we suggest that alternative regimens be clindamycin, 300 mg orally 2 times a day for 7 days, and metronidazole, 2 g orally in a single dose.

Factors other than effectiveness may influence providers or consumers to choose one product over another. Some health care providers prefer the intravaginal route of drug administration for treatment of BV because of lack of systemic side effects such as mild to moderate gastrointestinal upset and unpleasant taste (mean peak serum concentrations of metroni-

dazole following intravaginal administration are $<2\%$ those of standard, 500-mg oral doses, and mean bioavailability of clindamycin cream is about 4%) [28, 29]. Some women prefer to take oral medication because it is easier to use, less messy, and more convenient [30].

Treatment of BV in Pregnant Women

Only recently has BV been considered a syndrome with many clinically significant sequelae. For pregnant women, BV is associated with low birth weight, preterm birth, preterm labor, premature rupture of the membranes (PROM), chorioamnionitis, and postcesarean and postpartum endometritis [31–37]. Possible pathogenic factors for these sequelae include: (1) an increased number of potentially pathogenic microorganisms

Table 2. Summary of data from studies of bacterial vaginosis, in which a treatment regimen of metronidazole vaginal gel 0.75%, 5 g twice a day for 5 days, was compared with placebo.

Reference	Study design, population	Inclusion criteria	Cure definition	Follow-up visits*	Treatment regimen	Cure rate: % (no.) cured
[19]	RDB, 53 symptomatic nonpregnant women	$>20\%$ CC plus ≥ 2 of the following: HD, pH of >4.7 , and AO	$\leq 20\%$ CC plus absence of ≥ 2 of the following: HD, pH of >4.7 , and AO	4–16 d	Metro gel	87 (30)
				28–32 d	Placebo	17 (23)
					Metro gel	73 (30)
					Placebo	85 (26) [†]
[20]	RDB, 106 nonpregnant women	$\geq 20\%$ CC plus ≥ 2 of the following: HD, pH of >4.7 , and AO	$<20\%$ CC plus absence of ≥ 1 of the following: HD, pH of >4.7 , and AO	4–16 d	Metro gel	50 (4) [†]
				28–32 d	Placebo	78 (49)
					Metro gel	27 (41)
					Metro gel	69 (45)
					Placebo	91 (34) [†]
Summary				4–16 d	Metro gel	50 (8) [†]
				28–32 d		81 (79)
						71 (75)

NOTE. AO = amine odor; CC = clue cells; HD = homogeneous discharge; metro = metronidazole; RDB = randomized double-blind controlled trial.

* After completion of treatment.

[†] Among those cured at the first visit.

Table 3. Summary of studies comparing BV treatment of oral metronidazole 500 mg twice a day for 7 days with clindamycin vaginal cream 2%, 5 g at bedtime for 7 days, and metronidazole vaginal gel 0.75%, 5 g twice a day for 5 days.

Reference	Study design, population	Inclusion criteria	Cure definition	Follow-up visit*	Treatment regimen	Cure rate: % (no.) cured
[21]	RDB, 407 nonpregnant women	HD, pH of >4.5, AO, CC, GS(S)	Absence of 3 of the following: pH of >4.5, AO, and CC	5–10 d 25–39 d	Oral metro Cm Oral metro Cm	87 (110) 85 (124) 81 (106) 84 (123)
[22]	RDB, 60 symptomatic nonpregnant women	pH of >4.5, AO, CC, GS(S)	Absence of 3 of the following: pH of >4.5, AO, and CC	5–10 d 4 w	Oral metro Cm Oral metro Cm	83 (23) 96 (23) 94 (17) 89 (19)
[23]	RDB, 61 nonpregnant symptomatic women	pH of >4.5, AO, $\geq 20\%$ CC	Absence of symptom(s) plus absence of ≥ 2 of the following: pH of >4.5, AO, and $\geq 20\%$ CC	5–8 d 4 w	Oral metro Cm Oral metro Cm	87 (23) 72 (25) 61 (18) 61 (18)
[24]	RC, 101 nonpregnant symptomatic women	CC plus ≥ 2 of the following: pH of >4.5, AO, and HD	Absence of ≥ 3 of the following: pH of >4.5, AO, HD, and CC	7–10 d	Oral metro Cm Metro gel	84 (19) 86 (29) 75 (24)
[25, 26]	RSB, 112 nonpregnant women	$\geq 20\%$ CC plus ≥ 2 of the following: HD, pH of ≥ 4.7 , and AO	<20% CC plus absence of ≥ 2 of the following: HD, pH of ≥ 4.7 , and AO	1 w 4 w	Oral metro Metro gel Oral metro Metro gel	85 (47) 84 (43) 71 (45) 71 (41)
Summary				5–10 d 4 w	Oral metro Cm Metro gel Oral metro Cm Metro gel	86 (222) 85 (201) 81 (67) 78 (186) 82 (160) 71 (41)

NOTE. AO = amine odor; CC = clue cells; Cm = clindamycin cream; GS(N) = positive gram stain (by Nugent's method); GS(S) = positive gram stain (by Spiegel's method); HD = homogeneous discharge; metro = metronidazole; RC = randomized controlled trial; RDB = randomized double-blind controlled trial; RSB = randomized single-blind controlled trial.

* After completion of treatment.

for ascending infections; (2) a lower vaginal tissue redox potential and an elevated vaginal pH, both of which increase the infective potential of other pathogens [38]; (3) the presence of metabolic products and enzymes produced by abnormal vaginal flora that may significantly reduce leukocytes' ability to hinder infection and that may facilitate ascending infection [39, 40]; and (4) the presence of increased levels of endotoxin, which may act to stimulate a local cytokine response, resulting in production of prostaglandin [41, 42].

All women with symptomatic BV, whether pregnant or not, should receive therapy for BV to alleviate symptoms [43]. While the prevention of possible effects of symptomatic BV on a pregnancy (preterm birth, preterm labor, PROM, low birth weight, and chorioamnionitis) or the prevention of subsequent uterine infection (endometritis) would be a desirable result of such treatment, the result of such a strategy has not been well studied, and treatment should not be given simply to prevent these possible complications.

Thus, whether to treat pregnant women with asymptomatic BV is far more controversial, as there is no immediate therapeutic benefit to the woman; the goal of the identification and treatment of these women would be to prevent the adverse outcomes of pregnancy or to prevent subsequent endometritis. Of the clinical sequelae of BV in the pregnant woman cited above, only the prevention of preterm birth, PROM, and low birth weight have been studied in clinical trials, and those trials have not always separated symptomatic from asymptomatic women. The results are inconclusive but do suggest a different therapeutic approach for women who are at high risk for an adverse outcome (i.e., those with a preceding preterm birth) than for those women who are not at high risk (i.e., those with no such history). We recommend evaluation of high-risk pregnant women for asymptomatic BV, and for those who test positive, treatment with oral metronidazole (figure 1).

Table 4 summarizes studies evaluating the effects of treatment for BV (with oral and intravaginal regimens) on adverse

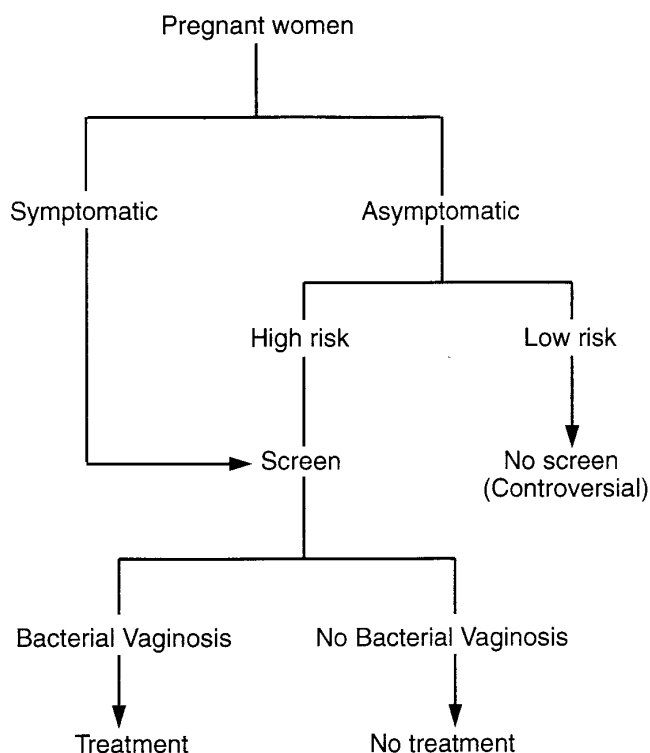


Figure 1. A paradigm for treatment of bacterial vaginosis in pregnant women.

outcomes of pregnancy (preterm birth, low birth weight, and PROM) [40, 44–48]. Data on universal screening for and treatment of BV in low-risk pregnant women, whether asymptomatic or symptomatic, are limited. The only published study that evaluated the effects of systemic treatment on asymptomatic low-risk pregnant women was a prospective controlled trial of BV screening and treatment conducted by McGregor et al. (table 4) [48]. Although this prospective controlled trial of women with asymptomatic BV showed a reduction of about 50% in the rate of preterm birth or PROM after treatment with oral clindamycin vs. no treatment, a randomized double-blind placebo-controlled trial is needed before universal screening and treatment for asymptomatic BV during pregnancy can be recommended for low-risk pregnant women.

Two studies show that treatment of high-risk pregnant women (not separated into symptomatic or asymptomatic women) with BV reduces preterm births (table 4) [44, 45]. Therefore, asymptomatic pregnant high-risk women may benefit from evaluation for BV and subsequent treatment. However, while some authorities currently recommend evaluation of high-risk pregnant women for asymptomatic BV (and treatment if they test positive), more clinical trial data are needed because the two studies on which this recommendation would be based had limitations [44, 45].

The first study, by Morales et al. [44], included only 80 evaluable women who were at high risk of preterm birth on

the basis of their pregnancy history; thus, sample size was small. The second study, by Hauth et al. [45], had the following limitations: (1) BV was treated with both oral metronidazole and erythromycin (making unclear what therapy with metronidazole alone would achieve); (2) the BV aspect of the trial was a post-hoc analysis; and (3) the study population comprised black lower-socioeconomic-status urban patients who might not be representative of the United States population.

Preliminary findings of a small Australian BV treatment trial indicate that the reduction in preterm births due to therapy for BV with oral metronidazole during the second trimester occurred mainly among asymptomatic high-risk women (women with a prior preterm birth); there was no reduction in the incidence of preterm birth among asymptomatic low-risk women with BV who received oral metronidazole [49]. To clarify the benefit of therapy for both low- and high-risk women, a large randomized clinical trial of treatment for asymptomatic BV in pregnant women in the United States population is under way (personal communication, National Institutes of Health, NICHD Maternal-Fetal Medicine Units Network).

Further work, in addition to these three trials [44, 45, 49], has suggested not only that high-risk pregnant women may benefit from evaluation and therapy but also that the type of therapy (systemic or topical) may be of importance. These studies indicate that treatment for BV during pregnancy with intravaginal clindamycin cream did not prevent preterm birth, but treatment with systemic clindamycin regimens might prevent preterm birth among pregnant women with an idiopathic preterm labor and who have received a parenteral tocolytic agent [40, 46, 47]. Presumably, the rationale for this difference is that systemic therapy acts against infection of the uterine cavity and its contents, which may be subclinical, while topical therapy is unable to do this. However, intravaginal clindamycin cream may cause a transient increase in high-density vaginal colonization by *Escherichia coli* [17], and a recent study has reported an association between high-density vaginal *E. coli* colonization and an increased risk of preterm birth [50].

Some health care providers remain concerned about the possible mutagenicity and teratogenicity of metronidazole, the former of which has been suggested by experiments on animals in which extremely high doses and prolonged dosing were used. However, recent reviews and meta-analyses of the use of metronidazole by humans revealed no evidence of mutagenicity [51, 52]. A possible teratogenic effect of metronidazole in humans has been suggested by two published case series, involving three cases of midline facial defects after metronidazole treatment at 5 and 7 weeks of gestation [53, 54]. A recent review on the potential for teratogenicity of metronidazole in humans revealed no evidence of teratogenicity [55].

As a general precaution, we believe screening and treatment, if they are to be done, should be conducted at the earliest part of the second trimester of pregnancy after organogenesis is complete. We also believe lower doses of medication in preg-

Table 4. Summary of data from studies investigating effects of treatment for bacterial vaginosis (BV) on adverse outcomes of pregnancy.

Reference	Study design, population	Inclusion criteria	Time of treatment	Treatment (no. of patients)	Outcome for indicated % (no. of recipients)
[44]	RDB, 94 pregnant women with preterm birth in preceding pregnancy	HD, pH of >4.5, CC, AO, PPB, and no TRICH	16–20 w of gestation	Metro, 250 mg t.i.d. for 7 d (44) Placebo: vitamin C (36)	Preterm birth at <34 w Metro: 5 Placebo: 11 Preterm birth at <37 w Metro: 18* Placebo: 39 Birth weight of <2,500 g Metro: 14* Placebo: 33 PROM Metro: 5* Placebo: 33
[45]	RDB, women with previous spontaneous preterm birth or weighing <50 kg before pregnancy	Three of the following: HD, pH of >4.5, CC, and AO plus no GC, yeast, or TRICH	Initial Rx: 22–24 w of gestation Second Rx (for those with BV): 2–4 w after completion of initial Rx	Metro, 250 mg t.i.d. for 7 d, plus Em, 333 mg t.i.d. for 14 d (433) Placebo: lactose filler (191)	Preterm birth at <37 w Among women with BV Treatment: 31 (172)* Placebo: 49 (86) Among women with BV and PPB Treatment: 39 (121)* Placebo: 57 (56) Among women with BV and weight of <50 kg Treatment: 14 (51)* Placebo: 33 (30) Among women without BV Treatment: 22 (254) Placebo: 25 (104)
[46]	RDB, 745 pregnant women with BV	GS(N), pH of >4.5	14–26 w of gestation	Cm 2%, 5 g at bedtime for 7 d (340) Placebo: vehicle of the cream (341)	Preterm birth at <37 w Cm: 15.0 Placebo: 13.5 Preterm birth at <32 w Cm: 4.7 Placebo: 2.6 Low birthweight (<2,500 g) Cm: 9.0 Placebo: 6.8
[40]	RDB, 142 pregnant women	>20% CC, plus ≥ 2 of the following: pH of >4.5, AO, and HD plus GS(N)	16–27 w of gestation	Cm 2%, 5 g at bedtime for 7 d (60) Placebo (69)	Preterm birth at <37 w Cm: 15.0 Placebo: 7.2 Low birth weight (<2,500 g) Cm: 13.6 Placebo: 4.4 PROM Cm: 15.0 Placebo: 16.2
[47]	RDB, 117 women who had preterm labor at ≤ 34 w and were treated with tocolytic drug	GS(S), idiopathic preterm labor, receipt of parenteral tocolytic drug, ≤ 34 w of gestation	≤ 34 w of gestation	Cm, 900 mg iv for 9 doses, followed by oral Cm, 300 mg q.i.d. for 4 d (53) Placebo: saline solution and lactose filler (50)	Among the 25 women with BV Mean birth weight Cm: 2,634 g Placebo: 2,296 g Mean increase in duration of pregnancy Cm: 36 d Placebo: 19 d
[48]	Prospective comparative controlled trials Phase I: no treatment for asymptomatic BV but treatment for symptomatic BV Phase II: treatment for asymptomatic and symptomatic BV	Two of the following: pH of >4.5, >20% CC, AO	First, second, and third trimester	For BV: 300 mg of oral Cm b.i.d. for 7 d; for other infections: CDC treatment guidelines followed; phase I: 614 women (171 with BV), phase II: 640 women (194 with BV)	Among women with BV Preterm birth at <37 w Phase I = 18.8,* phase II = 9.8 Preterm PROM Phase I = 6.9, phase II = 3.5 Among women with BV and prior preterm birth Preterm birth at <37 w Phase I = 46.2, phase II = 25.0

NOTE. AO = amine odor; CC = clue cells; CDC = Centers for Disease Control and Prevention; Cm = clindamycin; Em = erythromycin; GC = gonorrhea; GS(N) = positive gram stain (by Nugent's method); GS(S) = positive gram stain (by Spiegel's method); HD = homogeneous discharge; metro = metronidazole; PPB = previous preterm birth; PROM = premature rupture of membranes; RDB = randomized double-blind controlled trial; TRICH = trichomoniasis.

* $P < .05$.

nancy are preferable because of the general desire to limit the exposure of the fetus to medication. Because there are limited data on the dosage of metronidazole for treating BV during pregnancy, we recommend for high-risk pregnant women systemic therapy with metronidazole (for subclinical upper tract infection, to prevent adverse outcomes of pregnancy), at a dosage of 250 mg orally three times a day for 7 days (the dosage used in the studies of Morales et al. [44] and Hauth et al. [45]).

We do not recommend a regimen of 500 mg twice a day for 7 days for pregnant women because no published study has utilized this 500-mg regimen for pregnant women. Thus, we do not know the efficacy and safety of this 500-mg regimen for pregnant women or whether this regimen is just as or more efficacious than the 250-mg regimen. Because our recommendation is based on published articles concerning a regimen that has been studied in pregnant women, we recommend for pregnant women the dosage of 250 mg three times a day for 7 days. This dosage is comparable to that of 375 mg twice a day, which has an MIC₉₀ (minimum inhibitory concentration for ≥90% of the strains) of 2.0–4.0 µg/mL for *Bacteroides* species [56] and a mean peak plasma concentration of 10.9 µg/mL (G. D. Searle & Co., unpublished data). The alternative regimens are metronidazole, 2 g orally in a single dose, and clindamycin, 300 mg orally 2 times a day for 7 days; these regimens have not been examined for use in pregnancy.

Low-risk pregnant women (those without a prior preterm birth) with symptomatic disease should be treated to relieve the symptoms. The recommended regimen is metronidazole, 250 mg orally three times a day for 7 days. The alternatives are metronidazole (2 g orally in a single dose), clindamycin (300 mg orally 2 times a day for 7 days), and metronidazole gel (0.75%, one full 5-g applicator intravaginally, 2 times a day for 5 days). Some experts prefer the use of systemic therapy for low-risk women, to act against possible subclinical upper tract infection. We do not recommend the use of clindamycin vaginal cream in pregnancy, because two randomized trials showed a trend toward increased preterm births after treatment with clindamycin vaginal cream (table 4) [40, 46].

Treatment of Sex Partners

Because male sex partners should be treated if this results in improved cure rates in females, we examined studies that addressed this issue. Since our last review [7], no other studies of this issue have been reported. Thus, our previous recommendation (based on three studies showing no improvement in cure rates in association with treatment of sex partners [57–59]) that sex partners should not be treated remains. However, some clinicians favor doing so when women have intractable or recurrent disease.

Treatment of BV in Asymptomatic Patients in Surgical Settings

A randomized controlled trial has shown that treatment of asymptomatic patients with BV should be considered before a

surgical abortion procedure to prevent postabortal endometritis [60]. In this study, women undergoing first-trimester legal abortion were evaluated for BV. The week before the procedure, women with BV were randomized to receive either oral metronidazole (500 mg three times daily for 10 days) or a placebo. Among 174 evaluable women, 3.8% in the metronidazole group developed pelvic inflammatory disease, vs. 12.2% in the placebo group ($P < .05$).

On the basis of these data, it seems reasonable to recommend that all women about to undergo a surgical abortion be evaluated for BV. Those women with BV (symptomatic or asymptomatic) should be considered for treatment before performance of a surgical abortion procedure. However, more data are needed concerning treatment of asymptomatic patients with BV when other surgical or invasive procedures are planned.

New Metronidazole Formulation

Recently, the U.S. Food and Drug Administration approved Flagyl ER (G.D. Searle & Co., Skokie, IL), containing 750 mg of metronidazole, for the treatment of BV. The Flagyl ER tablet is an extended-release formulation that allows for once-daily dosing. No comparison studies of the use of Flagyl ER for the treatment of BV have been published yet. The manufacturer of Flagyl ER reported that in two randomized controlled trials, Flagyl ER administered once a day for 7 days cured 61% and 62% of patients with BV, 28–32 days post-therapy (G.D. Searle & Co, unpublished data). The clinical cure rate was similar to the cure rate among patients with BV treated with 2% clindamycin cream (5 g once a day for 7 days) in the first trial (61% vs. 59%) and was greater in the second trial (62% vs. 43%). With publication of the Flagyl ER studies, this formulation may be recommended in future reviews.

Discussion

Because BV is a polymicrobial infection, evaluating the success of treatment is complex, and approaches have varied widely among studies. In 1992 Larsson [14] reviewed published studies of treatment of BV and cited the following main issues that complicated the interpretation of treatment efficacy: (1) differences in diagnostic criteria for BV before or after treatment, (2) differences in exclusion criteria for treatment, (3) differences in evaluation time after treatment, (4) differences in treatment of sex partners, and (5) differences in the designs of the studies. All these issues make interstudy comparison difficult, although intrastudy comparisons of different treatment regimens would be far less affected. Despite these limitations, we believe there is sufficient consistency between and within studies to make valid conclusions.

We conclude that for nonpregnant women with BV, the recommended regimens are metronidazole, 500 mg orally twice daily for 7 days; clindamycin vaginal cream 2%, once daily for 7 days; and metronidazole vaginal gel 0.75%, twice daily

for 5 days; the alternative regimens are metronidazole, 2 g orally in a single dose, and clindamycin, 300 mg orally 2 times a day for 7 days.

For pregnant high-risk women, the objective of the treatment is to prevent adverse outcomes of pregnancy, in addition to relieving symptoms. Thus, systemic therapy against possible subclinical upper tract infection to prevent adverse outcomes of pregnancy is the preferable route of administration. In addition, lower doses of medication are preferable for pregnant women, to minimize exposure to the fetus. Data on the dosage of metronidazole to treat BV during pregnancy are limited. Since our last review [7], only two randomized controlled trials among pregnant women have been conducted in which systemic therapy (with metronidazole, 250 mg orally three times a day for 7 days) was given for BV [44, 45].

On the basis of this information, for pregnant high-risk women (symptomatic or asymptomatic), we recommend metronidazole at a dosage of 250 mg orally three times a day for 7 days or, alternatively, a single 2-g dose of metronidazole orally or clindamycin, 300 mg orally 2 times a day for 7 days. For pregnant low-risk women with symptomatic diseases, the main objective of the treatment is to relieve symptoms. We recommend for these women a regimen of metronidazole at 250 mg orally three times a day for 7 days or, alternatively, a regimen of metronidazole at 2 g orally in a single dose, clindamycin at 300 mg orally 2 times a day for 7 days, or metronidazole gel 0.75%, one full applicator (5 g) intravaginally, 2 times a day for 5 days.

Screening and treating women (symptomatic or asymptomatic) for BV before performing surgical abortion would be prudent to prevent postabortal endometritis; whether this recommendation can be extended to other gynecologic surgical procedures requires study.

References

- Eschenbach DA, Hillier SL, Critchlow C, Steven C, DeRouen T, Holmes KK. Diagnosis and clinical manifestation of bacterial vaginosis. *Am J Obstet Gynecol* **1988**;158:819–28.
- Thomason JL, Gelbart SM, Wilcoski LM, Peterson AK, Jilly BJH. Proline aminopeptidase activity as a rapid diagnostic test to confirm bacterial vaginosis. *Obstet Gynecol* **1988**;71:607–11.
- Hillier SL, Krohn MA, Rabe LK, Klebanoff SJ, Eschenbach DA. The normal vaginal flora, H₂O₂-producing lactobacilli, and bacterial vaginosis in pregnant women. *Clin Infect Dis* **1993**;16(suppl 4):S273–81.
- Barbone F, Austin H, Louw WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. *Am J Obstet Gynecol* **1990**;163:510–4.
- Avonts D, Sercu M, Heyerick P, Vandermeeren I, Meheus A, Piot P. Incidence of uncomplicated genital infections in women using oral contraception or an intrauterine device: a prospective study. *Sex Transm Dis* **1990**;17:23–9.
- Hawes SE, Hillier SL, Benedetti J, et al. Hydrogen peroxide-producing lactobacilli and acquisition of vaginal infections. *J Infect Dis* **1996**;174:1058–63.
- Joesoef MR, Schmid GP. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis* **1995**;20(suppl 1):S72–9.
- Amsel R, Totten PA, Spiegel CA, Chen KCS, Eschenbach DA. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. *Am J Med* **1983**;74:14–22.
- Dunkelberg WE. Diagnosis of *Haemophilus vaginalis* vaginitis by gram-stained smears. *Am J Obstet Gynecol* **1965**;91:998–1000.
- Spiegel CA, Amsel R, Holmes KK. Diagnosis of bacterial vaginosis by direct gram stain of vaginal fluid. *J Clin Microbiol* **1983**;18:170–7.
- Nugent RP, Krohn MA, Hillier SL. The reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol* **1991**;29:297–301.
- Joesoef MR, Hillier SL, Josodiwondo S, Linnan M. Reproducibility of a scoring system for gram stain diagnosis of bacterial vaginosis. *J Clin Microbiol* **1991**;29:1730–1.
- Schwebke JR, Hillier SL, Sobel JD, McGregor JA, Sweet RL. Validity of the vaginal gram stain for the diagnosis of bacterial vaginosis. *Obstet Gynecol* **1996**;88:573–6.
- Larsson P-G. Treatment of bacterial vaginosis. *Int J STD AIDS* **1992**;3:239–47.
- Rein MF, Holmes KK. Nonspecific vaginitis, vulvovaginal candidiasis and trichomoniasis. *Current Clin Top Infect Dis* **1983**:292–304.
- McCarthy LR, Mickelsen P, Smith E. Antibiotic susceptibility of *Haemophilus vaginalis* (*Corynebacterium vaginale*) to 21 antibiotics. *Antimicrob Agents Chemother* **1979**;16:186–9.
- Hillier S, Krohn MA, Watts DH, Wolner-Hanssen P, Eschenbach D. Microbiologic efficacy of intravaginal clindamycin cream for the treatment of bacterial vaginosis. *Obstet Gynecol* **1990**;76:407–13.
- Stein GE, Christensen SL, Mummaw NL, Soper DE. Placebo-controlled trial of intravaginal clindamycin 2% cream for the treatment of bacterial vaginosis. *Ann Pharmacother* **1993**;27:1343–5.
- Hillier SL, Lipinski C, Briselden AM, Eschenbach DA. Efficacy of intravaginal 0.75% metronidazole gel for the treatment of bacterial vaginosis. *Obstet Gynecol* **1993**;81:963–7.
- Livengood CH 3rd, McGregor JA, Soper DE, Newton E, Thomason JL. Bacterial vaginosis: efficacy and safety of intravaginal metronidazole treatment [see comments]. *Am J Obstet Gynecol* **1994**;170:759–64.
- Fischbach F, Petersen EE, Weissenbacher ER, Martius J, Hosmann J, Mayer H. Efficacy of clindamycin vaginal cream versus oral metronidazole in the treatment of bacterial vaginosis. *Obstet Gynecol* **1993**;82:405–10.
- Andres FJ, Parker R, Hosein I, Benrubi GI. Clindamycin vaginal cream versus oral metronidazole in the treatment of bacterial vaginosis: a prospective double-blind clinical trial. *South Med J* **1992**;85:1077–80.
- Schmitt C, Sobel JD, Meriwether C. Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. *Obstet Gynecol* **1992**;79:1020–3.
- Ferris DG, Litaker MS, Woodward L, Mathis D, Hendrich J. Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. *J Fam Pract* **1995**;41:443–9.
- Curatek Pharmaceuticals. MetroGel-Vaginal (metronidazole vaginal gel): effective intravaginal therapy for bacterial vaginosis. A clinical monograph. Elk Grove Village, IL: Curatek Pharmaceuticals, **1996**:17–8.
- McGregor JA, Hillier SL, Eschenbach DA, et al. Efficacy of MetroGel-Vaginal versus oral metronidazole for treatment of bacterial vaginosis: a randomized, single-blind parallel comparison [abstract no 3]. Presented at the 11th Meeting of the International Society of Sexually Transmitted Diseases Research (New Orleans). **1995**.
- Greaves WL, Chungafung J, Morris B, Haile A, Townsend JL. Clindamycin versus metronidazole in the treatment of bacterial vaginosis. *Obstet Gynecol* **1988**;72:799–802.
- Cunningham FE, Kraus DM, Brubaker L, Fischer JH. Pharmacokinetics of intravaginal metronidazole gel. *J Clin Pharmacol* **1994**;34:1060–5.

29. Borin MT, Powley GW, Tackwell KR, Batts DH. Absorption of clindamycin after intravaginal application of clindamycin phosphate 2% cream. *J Antimicrob Chemother* **1995**;35:833–41.
30. Vaginal infections. Roper Starch Worldwide, **1996**:1–24.
31. Faro S, Phillips LE, Martens MG. Perspectives on the bacteriology of postoperative obstetric-gynecologic infections. *Am J Obstet Gynecol* **1988**;158(suppl):694–700.
32. Hillier SL, Martius J, Krohn MA, Kiviat NB, Holmes KK, Eschenbach DA. Case-control study of chorioamnionic infection and chorioamnionitis in prematurity. *N Engl J Med* **1988**;319:972–5.
33. Watts D, Krohn M, Hillier S, Eschenbach D. Bacterial vaginosis as a risk factor for postcesarean endometritis. *Obstet Gynecol* **1990**;75:52–8.
34. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and *Chlamydia trachomatis* infection with adverse pregnancy outcome. *JAMA* **1986**;256:1899–903.
35. Gravett MG, Hummel D, Eschenbach DA, Holmes KK. Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. *Obstet Gynecol* **1986**;67:229–37.
36. Newton ER, Pridoda TJ, Gibbs RS. A clinical and microbiologic analysis of risk factors for puerperal endometritis. *Obstet Gynecol* **1990**;75:402–6.
37. McGregor JA, French JI, Richter R, et al. Antenatal microbiologic and maternal risk factors associated with prematurity. *Am J Obstet Gynecol* **1990**;163:1465–73.
38. Holmes KK, Chen KCS, Lipinski CM, Eschenbach DA. Vaginal redox potential in bacterial vaginosis (nonspecific vaginitis). *J Infect Dis* **1985**;152:379–82.
39. Briselden M, Moncla B, Stevens C, Hillier S. Sialidases (neuraminidases) in bacterial vaginosis and bacterial vaginosis-associated microflora. *J Clin Microbiol* **1992**;30:663–6.
40. McGregor JA, French JI, Jones W, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. *Am J Obstet Gynecol* **1994**;170:1048–59.
41. Platz-Christensen JJ, Mattsby-Baltzer I, Thomsen P, Wiqvist N. Endotoxin and interleukin-1c in the cervical mucus and vaginal fluid of pregnant women with bacterial vaginosis. *Am J Obstet Gynecol* **1993**;169:1161–6.
42. Platz-Christensen JJ, Brandberg A, Wiqvist N. Increased prostaglandin concentrations in the cervical mucus of pregnant women with bacterial vaginosis. *Prostaglandins* **1992**;43:133–4.
43. Centers for Disease Control and Prevention. 1993 Sexually transmitted diseases treatment guidelines. *MMWR Morb Mortal Wkly Rep* **1993**;42:27–46.
44. Morales WJ, Schom S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. *Am J Obstet Gynecol* **1994**;171:345–9.
45. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Mid-trimester treatment with metronidazole plus erythromycin reduces preterm delivery only in women with bacterial vaginosis [abstract]. *Am J Obstet Gynecol* **1995**;172:253.
46. Joesoef MR, Hillier SL, Wiknjosastro G, et al. Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight. *Am J Obstet Gynecol* **1995**;173:1527–31.
47. McGregor JA, French JI, Seo K. Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial. *Am J Obstet Gynecol* **1991**;165:867–75.
48. McGregor JA, French JI, Parker R, et al. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation [see comments]. *Am J Obstet Gynecol* **1995**;173:157–67.
49. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Metronidazole treatment of bacterial vaginosis in pregnancy and preterm birth: a randomized, placebo-controlled trial [abstract]. Presented at the Infectious Diseases Society Obstetrics and Gynecology Meeting (Beaver Creek, Colorado). **1996**.
50. Krohn MA, Thwin SS, Rabe LK, Brown Z, Hillier SL. Vaginal colonization by *Escherichia coli* as a risk factor for very low birth weight delivery and other perinatal complications. *J Infect Dis* **1997**;175:606–10.
51. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* **1995**;172:525–9.
52. Schwebke JR. Metronidazole: utilization in the obstetric and gynecologic patient. *Sex Transm Dis* **1995**;22:370–6.
53. Cantu JM, Garcia-Cruz D. Midline facial defect as a teratogenic effect of metronidazole. *Birth Defects* **1982**;18:85–8.
54. Greenberg F. Possible metronidazole teratogenicity and clefting. *Am J Med Genet* **1985**;22:825.
55. Struthers BJ. Metronidazole appears not to be a human teratogen: review of literature. *Infect Dis Obstet Gynecol* **1997**;5:326–35.
56. Hasselquist MB, Hillier S. Susceptibility of upper-genital-tract isolates from women with pelvic inflammatory disease to ampicillin, cefpodoxime, metronidazole, and doxycycline. *Sex Transm Dis* **1991**;18:146–9.
57. Vejtorp M, Bollerup AC, Vejtorp L, et al. Bacterial vaginosis: a double-blind randomized trial of the effect of treatment of the sexual partner. *Br J Obstet Gynecol* **1988**;95:920–6.
58. Moi H, Erkkola R, Jerve F, et al. Should male consorts of women with bacterial vaginosis be treated? *Genitourin Med* **1989**;65:263–8.
59. Mengel MB, Berg AO, Weaver CH, et al. The effectiveness of single-dose metronidazole therapy for patients and their partners with bacterial vaginosis. *J Fam Pract* **1989**;28:163–71.
60. Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Pahlson C. Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind, randomized study. *Am J Obstet Gynecol* **1992**;166:100–3.