

Antibiotics for Bacterial Vaginosis or *Trichomonas vaginalis* in Pregnancy: A Systematic Review

Nan Okun, MD, Karen A. Gronau, MSc, MD, and Mary E. Hannah, MDCM

OBJECTIVE: To determine whether antibiotic treatment for bacterial vaginosis or *Trichomonas vaginalis* during pregnancy decreases the risk of preterm birth and associated adverse outcomes.

DATA SOURCES: Pre-MEDLINE and MEDLINE (1966–2003), EMBASE (1980–2003), and the Cochrane Library were searched using the keywords “bacterial vaginosis,” “*Trichomonas*,” “*Trichomonas vaginalis*,” “*Trichomonas vaginitis*,” “*Trichomonas infections*,” “pregnancy,” “pregnant,” “antibiotics,” and “antibiotic prophylaxis.”

METHODS OF STUDY SELECTION: The search produced 1,888 titles, of which 1,256 abstracts were reviewed further. Of these, 1,217 were ineligible. Inclusion criteria were the following: randomized controlled trials in which antibiotics were compared with no antibiotic or placebo, for women in the second or third trimester of pregnancy with symptomatic or asymptomatic bacterial vaginosis or *Trichomonas vaginalis*, intact membranes, and not in labor. Exclusion criteria were as follows: published in a language other than English, dropout rate of more than 20% of women in either group, and lack of usable outcomes. Of the 39 papers reviewed in detail, 14 studies were included in the meta-analysis.

TABULATION, INTEGRATION, AND RESULTS: One of the authors reviewed titles obtained from the searches, and 2 reviewers independently reviewed the abstracts, excluded those that were ineligible, identified eligible papers, and abstracted the data. For women with bacterial vaginosis, antibiotics reduced the risk of persistent infection but did not reduce the risk of preterm birth or the incidence of associated adverse outcomes for the general population or for any subgroup analyzed. For women with *Trichomonas vaginalis*, metronidazole reduced the risk of persistent infection but increased the incidence of preterm birth.

CONCLUSION: Contrary to the conclusions of 3 recent systematic reviews, we found no evidence to support the use of antibiotic treatment for bacterial vaginosis or *Trichomonas vaginalis* in pregnancy to reduce the risk of preterm birth or its associated morbidities in low- or high-risk women.

From the Departments of Obstetrics and Gynaecology, Mount Sinai Hospital, and Sunnybrook and Women's College Health Sciences Centre, Toronto; and Maternal Infant and Reproductive Health Research Unit at the Centre for Research in Women's Health, University of Toronto, Toronto, Ontario, Canada.

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Preterm birth is responsible for a substantial proportion of perinatal mortality and long-term infant morbidity.¹ The rate of preterm birth has increased over the past several decades, despite a growing understanding of the risk factors and etiologies of this problem. It has been recognized for some time that infection of the fetal membranes and/or the amniotic fluid is associated with preterm birth, particularly births occurring at less than 30 weeks of gestation.² One of the proposed etiologies of intrauterine infection is ascension of organisms from the vagina into the uterus.³

Both bacterial vaginosis and *Trichomonas vaginalis* in pregnancy have been shown to be associated with preterm labor and preterm birth.^{4–9} With bacterial vaginosis, the proportion of normal lactobacilli is decreased, with resultant overgrowth of other organisms, including *Gardnerella vaginalis*, *Mobiluncus*, and anaerobes. Studies have shown that the risk of preterm birth is increased when bacterial vaginosis is diagnosed early rather than late in pregnancy.¹⁰ *Trichomonas vaginalis* is a sexually transmitted disease, with a prevalence of approximately 10%, depending on the population.⁹

If bacterial vaginosis and/or *Trichomonas vaginalis* are associated with preterm labor and birth, it is possible that antibiotic treatment of these organisms would reduce the risk of this adverse outcome. Three meta-analyses have been recently published on the treatment of bacterial vaginosis; all have concluded that there is no benefit to screening and treatment of bacterial vaginosis among the general obstetric population. However, all 3 continue to suggest that there is benefit to screening and treatment of women at high risk for preterm birth.^{11–13}

The most recent Cochrane review on the treatment of *Trichomonas vaginalis* has concluded that there is no benefit from treatment with antibiotics and suggests that there may be a possible harmful effect because the largest trial was stopped early due to an increased risk of preterm birth with metronidazole treatment.¹⁴



More randomized controlled trials have since been published, perhaps altering the conclusions of the above reviews. We therefore undertook this systematic review and meta-analysis of randomized controlled trials of antibiotic treatment for pregnant women with either bacterial vaginosis or *Trichomonas vaginalis* to determine whether antibiotic therapy reduced the risk of preterm birth or associated adverse outcomes among pregnant women with either of these conditions.

SOURCES

Pre-MEDLINE and MEDLINE (1966–2003), EMBASE (1980–2003), and the Cochrane Library were searched using the keywords “bacterial vaginosis,” “*Trichomonas*,” “*Trichomonas vaginalis*,” “*Trichomonas vaginitis*,” “*Trichomonas* infections,” “pregnancy,” “pregnant,” “antibiotics,” and “antibiotic prophylaxis.” All searches were limited to female human subjects.

STUDY SELECTION

Studies were considered eligible for inclusion in the review if they were randomized controlled trials in which antibiotics were compared with no antibiotic or placebo, for women with symptomatic or asymptomatic bacterial vaginosis or *Trichomonas vaginalis*, as defined by each author’s diagnostic criteria. Studies were eligible if women were not in labor, had intact membranes, and were in the second or third trimester of pregnancy at the time of randomization. The primary outcome measure was preterm birth before 37 weeks of gestation. Secondary outcome measures were preterm birth before 35 weeks, 34 weeks, 32 weeks, or 28 weeks of gestation, low birth weight (< 2,500 g), very low birth weight (< 1,500 g), preterm prelabor rupture of the membranes (PPROM), chorioamnionitis, endometritis, peripartum infection, perinatal death, neonatal sepsis, and admission to a neonatal intensive care unit (NICU). Eradication of the organism from the vagina was also assessed. Studies were considered eligible if data were presented for eligible women, even if not all women met the eligibility criteria.

Studies were excluded if they were not reported in English and/or if the study design was not a randomized controlled trial. Studies were also excluded if more than 20% of women in either group in the trial were lost to follow-up or if there were no usable outcomes reported.

One of the authors (K.A.G.) reviewed titles obtained from the searches. Case reports, descriptive studies, studies published in abstract form only, commentaries, and letters to the editor were excluded. Two reviewers (K.A.G. and N.O.) independently reviewed all remain-

ing abstracts. If the reviewers agreed that an abstract described a study that was ineligible for the review, the abstract was excluded and the paper was not reviewed. If the reviewers were not in agreement or if they agreed that the study might be eligible, the paper was reviewed. Both reviewers (K.A.G. and N.O.) independently came to an assessment as to whether the paper was eligible for inclusion in the review. Disagreements were resolved by consensus or by discussion with a third party (M.E.H.). The reference lists of review papers and clinical practice guidelines were also reviewed for potentially eligible studies. Two reviewers (K.A.G. and N.O.) independently abstracted data from eligible papers.

The search produced 1,888 titles. Of these 1,256 abstracts were selected for further review. Of those abstracts reviewed, 1,217 were excluded because they clearly did not meet eligibility criteria.

The papers for the remaining 39 abstracts were reviewed in detail. Of these, 25 studies were excluded for the following reasons: 4 studies were not randomized,^{9,15–17} in 4 studies more than 20% of randomized subjects were lost to follow up,^{18–21} in 5 studies there were no data available on the outcomes of interest or data were not presented separately for bacterial vaginosis or *Trichomonas vaginalis*,^{22–26} 4 studies excluded pregnant women,^{27–30} 1 study included only women with ruptured membranes or women in preterm labor,³¹ in 2 studies all culture-positive women were treated,^{32,33} and 4 studies presented data that were published elsewhere.^{34–37} A recently published study of *Trichomonas vaginalis* treatment during pregnancy³⁸ was excluded because it was a subanalysis of a larger trial of mass treatment of sexually transmitted diseases to prevent human immunodeficiency virus (HIV) acquisition.³⁹ The remaining 14 papers met our eligibility criteria and were included in this systematic review.^{40–53}

Analyses

Baseline data for women enrolled in the trials were presented descriptively. The rates of preterm birth at less than 37 weeks of gestation and other outcomes were compared for the antibiotic and no antibiotic or placebo groups for all women who had bacterial vaginosis, irrespective of whether they were symptomatic or asymptomatic or were at low or high risk of preterm birth. Subgroup analyses for the outcome of preterm birth at less than 37 weeks were undertaken for women with bacterial vaginosis who were treated with different types of antibiotics, for women who had confirmed bacterial vaginosis at the time of randomization, and for women who were at high risk for preterm birth. Women at high risk for preterm birth were those with a history of spontaneous preterm birth (or with a history of any



preterm birth, if information on spontaneous preterm birth was not available) or second-trimester miscarriage.

The rates of preterm birth at less than 37 weeks and other outcomes were also compared between the antibiotic and the no antibiotic or placebo groups, among women who had *Trichomonas vaginalis*. Lastly, comparisons of each specific type of antibiotic with no antibiotic were undertaken, for women with either bacterial vaginosis or *Trichomonas vaginalis* in terms of the risk of preterm birth at less than 37 weeks.

Statistical analyses were undertaken with Review Manager 4.1.1 (The Cochrane Collaboration, Oxford, UK). We calculated a relative risk (RR) and 95% confidence interval (CI) for dichotomous variables using the DerSimonian and Laird random-effects model.⁵⁴ A random-effects model incorporates between-study variation and gives wider confidence intervals than a fixed-effects model, which ignores between-study variation in estimating CI. Results were considered statistically significant if the 95% CI did not encompass one for RR or if the *P* value was less than .05. Tests of heterogeneity among pooled results were conducted using simple χ^2 analysis.

RESULTS

Description of Studies

Overall, the studies were of high methodological quality in that the randomization sequence was likely concealed to some extent in all studies, because loss to follow-up was less than 5% in most studies and because all except one⁴¹ were placebo-controlled, thus minimizing bias in the assessment of outcomes. Concealment of the randomization sequence was likely to have occurred in 12 studies as double-masked allocation, with identical antibiotics and placebo, was described.^{40–50,52,53} Four studies specified that pharmacists had dispensed the medications in identical bottles.^{47,48,50,52} In one study,⁵¹ tablets in numbered, sealed, opaque envelopes were picked from a box. In one study,⁴⁴ tubes had coded allocation numbers that were kept by the data manager in a central location. Lastly, in 2 studies,^{45,52} allocations were kept in sealed opaque envelopes until the trial ended.

The type of placebo varied in the studies. Two studies used vitamin C tablets as placebo,^{50,51} whereas the other 11 studies used a placebo that was described as appearing identical to the antibiotic preparation.^{40,42–49,52,53}

The selection criteria and antibiotic regimens are shown in Table 1. Twelve studies evaluated the effect of antibiotics principally among women with bacterial vaginosis.^{40,42–45,47–53} In 2 of these, some women also had *Trichomonas vaginalis*.^{43,44} Two studies evaluated the effect of antibiotics principally among women with *Trichomonas vaginalis*,^{41,46} and in one of these studies some

women also had bacterial vaginosis.⁴⁶ In some studies, screening was performed in the first trimester as well as in the second trimester of pregnancy.^{42,45,46,50} Enrollment and randomization were limited to women in the second trimester of pregnancy in all but 2 studies.^{45,50}

Of the 11 studies that assessed antibiotics principally for bacterial vaginosis, 5 used metronidazole, 5 used clindamycin, and 1 study used a combination of metronidazole and erythromycin (Table 1). The 2 studies that assessed antibiotics principally for the treatment of *Trichomonas vaginalis* used metronidazole alone (Table 1). The antibiotic regimens used are outlined in Table 1. Baseline characteristics of antibiotic and control groups were similar in all studies (Table 2).

Antibiotics for Bacterial Vaginosis in Low- and High-Risk Women

Eradication of Bacterial Vaginosis. Five studies, as well as the pooled data from these studies, reported that antibiotics reduced the risk of persistent bacterial vaginosis (RR 0.32, 95% CI 0.20–0.52, *P* < .001) (Table 3).^{42–45,48}

Preterm Birth. Eleven studies that assessed the effect of antibiotic treatment for women with bacterial vaginosis included data on rates of preterm birth at less than 37 weeks of gestation.^{42–47,49–53} When results for all women were pooled, there was no difference between the antibiotic and placebo groups on the risk of preterm birth at less than 37 weeks (RR 0.93, 95% CI 0.70–1.22, *P* = .6) (Table 3 and Fig. 1). Antibiotic treatment also did not reduce the risk of preterm birth at less than 35 weeks,⁴² less than 34 weeks,^{40,50,51} less than 32 weeks,^{42,44,52} or less than 28 weeks⁵¹ among women with bacterial vaginosis (Table 3).

Preterm Birth at Less Than 37 Weeks Among Subgroups of Women. Among women with bacterial vaginosis considered to be at high risk because of a previous spontaneous preterm birth, a previous preterm birth, or a previous second-trimester miscarriage, pooled data revealed no effect of antibiotics on preterm birth at less than 37 weeks (RR 0.75, 95% CI 0.45–1.24, *P* = .30) (Table 4).^{42,43,47,50–52} Among women known to be positive for bacterial vaginosis at the time of both randomization and treatment (thus excluding women who spontaneously cleared the organism subsequent to screening), there was no effect of antibiotics on the risk of preterm birth at less than 37 weeks (RR 0.91, 95% CI 0.66–1.26, *P* = .60) (Table 4).^{42–44,46,47,50,51,53}

When only those trials that assessed the effect of metronidazole for women with bacterial vaginosis were included, the pooled data showed no effect of metroni-



Table 1. Selection Criteria and Antibiotic Regimens

Study Country (Year)	Principal Abnormality of Vaginal Flora Studied	Method of Diagnosis of Bacterial Vaginosis or <i>Trichomonas vaginalis</i> *	GA Eligible for Screening (GA at Randomization) (wk)	High vs Low Risk†	Other Selection Criteria	Antibiotic Regimen
Carey ⁴² U.S. (2000)	Bacterial vaginosis	Clinical criteria and Gram stain (Nugent's)	8–22 ⁶ (16 ⁰ –23 ⁶)	Both		Single dose oral metronidazole twice (48 h apart)
Hauth ⁴³ U.S. (1995)	Bacterial vaginosis	Clinical criteria and Gram stain	22–24 (22–24)	Both	Prior preterm birth or weight < 50 kg	Oral metronidazole and erythromycin for 7 days
McDonald ⁴⁸ Australia (1994)	Bacterial vaginosis	Direct smear (Spiegel's)	16–24 (~24)	Not stated		Oral metronidazole for 2 days
McDonald ⁴⁷ Australia (1997)	Bacterial vaginosis	Gram stain and culture	16–26 (24–24.1, mean)	Both	No vaginal symptoms	Oral metronidazole for 2 days
Morales ⁵⁰ U.S. (1994)	Bacterial vaginosis	Clinical criteria	13–20 (13–20)	High risk		Oral metronidazole for 7 days
Odendaal ⁵¹ South Africa (2002)	Bacterial vaginosis	Clinical criteria and Gram stain (Spiegel's)	15–26 (15–26)	Both	Primigravida or prior preterm birth or second trimester miscarriage	Oral metronidazole for 2 days
Joeseof ⁴⁴ Indonesia (1995)	Bacterial vaginosis	pH and Gram stain (Nugent's)	14–26 (14–26)	Both		Clindamycin vaginal cream for 7 days
Kekki ⁴⁵ Finland (2001)	Bacterial vaginosis	Gram stain (Nugent's and Spiegel's)	10–17 (12–19)	Low risk		Clindamycin vaginal cream for 7 days
McGregor ⁴⁹ U.S. (1994)	Bacterial vaginosis	Clinical criteria and Gram stain (Nugent's)	16–27 (16–27)	Both		Clindamycin vaginal cream for 7 days
Ugwumadu ⁵² U.K. (2003)	Bacterial vaginosis	Gram stain (Nugent's)	12–16 (15.6–15.7, mean)	Both		Oral clindamycin for 5 days
Ross ⁴¹ South Africa (1983)	<i>Trichomonas vaginalis</i>	<i>Trichomonas</i> microscopy	< 34 (< 34)	Not stated	"Normal" pregnancy	Single dose oral metronidazole
Klebanoff ⁴⁶ U.S. (2001)	<i>Trichomonas vaginalis</i>	<i>Trichomonas</i> culture	8–22 ⁶ (16–23 ⁶)	Both	<i>Trichomonas</i> culture-positive	Single dose oral metronidazole twice (48 h apart)
Lamont ⁵³ U.K. (2003)	Bacterial Vaginosis	Gram stain (Nugent)	13–20 (13–20)	Both		Clindamycin vaginal cream for 3 nights
Vermeulen ⁴⁰ The Netherlands (1999)	Bacterial vaginosis	Nugent score	< 26 (< 26)	High risk		Clindamycin vaginal cream for 7 nights

GA, gestational age.

* Clinical or Amsel's criteria included pH testing of vaginal swab (< 4.5), the presence of clue cells, a positive whiff or amine test and characterization of vaginal discharge (thin, white, homogeneous). Nugent's criteria is a score of > 6/10 derived from estimating the relative proportions of the bacterial morphotypes *Lactobacillus* (4+–0), *Mobiluncus* (0–2+), and *Gardnerella* (0–4+) in the vaginal smear (< 4 = normal, 4–6 = intermediate, and > 6 = bacterial vaginosis). Spiegel's criteria were similar to Nugent's criteria, except that slides were also read as positive if other morphotypes predominated, even if *Lactobacillus* was 3+ or more.

† Low risk = nulliparous women or multiparous women with no history of prior spontaneous preterm birth or prior preterm birth if spontaneous preterm birth was not specified or prior second-trimester miscarriage; high risk = women with a history of a prior spontaneous preterm birth or prior preterm birth if spontaneous preterm birth was not specified or prior second-trimester miscarriage.



Table 2. Numbers Analyzed and Baseline Characteristics

Study	No. of Patients Included in Analyses (Lost to Follow-up)		Nulliparous (%)		Previous Preterm Birth (%)		Maternal Age (Mean ± SD, y)	
	Antibiotic Group	Control Group	Antibiotic Group	Control Group	Antibiotic Group	Control Group	Antibiotic Group	Control Group
Carey ⁴²	953 (13)	966 (22)	46	42	11	11	23 ± 5	23 ± 6
Hauth ⁴³	433 (0)	191 (0)	19	16	39	39	23.6 ± 4.8	23.7 ± 4.9
McDonald ⁴⁸	30 (0)	36 (0)	NS	NS	NS	NS	NS	NS
McDonald ⁴⁷	429 (12)	428 (10)	32	34	5	6	25.9	26.6
Morales ⁵⁰	44*	36*	0	0	100	100	25.1 ± 4.4	24.4 ± 3.7
Odendaal ⁵¹	136 (5)	133 (3)	49	62	51	38	22.3 ± 4.9 (Nulliparous) 27.9 ± 5.4 (Multiparous)	21.2 ± 5.0 (Nulliparous) 27.2 ± 4.5 (Multiparous)
Joesoef ⁴⁴	340 [†]	341 [†]	29	26	12 [‡]	10 [‡]	35% < 25, 45% 25–30, 19% > 30	33% < 25, 48% 25–30, 18% > 30
Kekki ⁴⁵	187 (17)	188 (18)	NS	NS	0	0	28.7	28.7
McGregor ⁴⁹	60 (1)	69 (1)	1.0 [§]		10.9		23.8 [¶]	
Ugwumadu ⁵²	244 (5)	241 (5)	0.8 [§]		10	9	28.8 ± 5.6	28.5 ± 5.4
Ross ⁴¹	99 (11)	109 (6)	“Similar”		NS	NS	NS	
Klebanoff ⁴⁶	315 (5)	289 (8)	49	47	11	10	22.7 ± 5.8	22.9 ± 5.4
Lamont ⁵³	208 (0)	201 (0)	53	56	7	8	27 ± 5	27 ± 5
Vermeulen ⁴⁰	11 (0)	11 (0)	NS	NS	100	100	NS	NS

SD, standard deviation; NS, not specified.

* Fourteen women were lost from this study (not stated which group they were from).

† 64 women were lost from this study (not stated which group they were from).

‡ History of preterm delivery or low birth weight.

§ Mean parity.

|| Total number of subjects with prior preterm birth (not stated which group they were from).

¶ Mean age (women were 16–27 years of age).

dazole on preterm birth at less than 37 weeks (RR 1.08, 95% CI 0.73–1.59, $P = .70$) (Table 4).^{42,46,47,50,51} One study that assessed the combined effect of metronidazole and erythromycin did find a reduction in the risk of preterm birth at less than 37 weeks among women at high risk for preterm birth (RR 0.68, 95% CI 0.49–0.93, $P = .01$) (Table 4).⁴³

Similarly, when only those trials that assessed the effect of clindamycin for women with bacterial vaginosis were included, there was no overall effect of clindamycin on preterm birth at less than 37 weeks (RR 0.82, 95% CI 0.45–1.50, $P = .50$).^{44,45,49,52,53} However, 2 recently published studies of clindamycin reported a reduction in preterm birth. Lamont et al⁵³ included 409 women randomized to a 2-day course of vaginal clindamycin compared with placebo between 13 and 20 weeks of gestation (RR 0.41, 95% CI 0.18–0.91, $P = .03$). Ugwumadu et al⁵² included 485 women at a mean gestational age of 15.6 weeks and randomized them to a 5-day course of oral clindamycin compared with placebo (RR 0.39, 95% CI 0.20–0.76, $P = .005$).

Other Outcomes. Ugwumadu et al⁵² found a significantly lower rate of second-trimester miscarriage in the

clindamycin group (RR 0.20, 95% CI 0.04–0.89, $P = .04$) among women with bacterial vaginosis detected and treated between 12 and 16 weeks of gestation (Table 4). Antibiotic treatment did not reduce the risk of low birth weight (< 2,500 g),^{42,44,49,50,52,53} or very low birth weight (< 1,500 g) infants,^{42,52,53} admission to a NICU,^{47,52} perinatal death,^{51,52,53} prelabor rupture of the membranes (RR 0.57 95% CI 0.22–1.47, $P = .06$),⁵⁰ or peripartum infection among women with bacterial vaginosis (Table 4).⁴⁵

Antibiotics for *Trichomonas vaginalis* in Low- and High-Risk Women

Eradication of *Trichomonas vaginalis*. Three studies reported on this outcome,^{41,43,46} but the Ross and Van Middlekoop⁴¹ study sustained a greater than 20% loss to follow-up in the untreated group, and the data were therefore not included in our meta-analysis. The pooled data from the 2 remaining studies^{43,46} demonstrated a significant reduction in the persistence of *Trichomonas vaginalis* with antibiotic treatment (RR 0.18, 95% CI 0.07–0.48, $P < .001$).



Table 3. Treatment of Bacterial Vaginosis With Any Antibiotic Compared With No Antibiotics

Outcome/Study	No. With Outcome/No. Randomized		Relative Risk (95% CI)
	Antibiotic Group	Control Group	
Persistent bacterial vaginosis			
Carey ⁴²	188/245	538/859	0.36 (0.31–0.41)
Hauth ⁴³	53/176	71/87	0.37 (0.29–0.47)
Joesoef ⁴⁴	15/340	152/341	0.10 (0.06–0.16)
Kekki ⁴⁵	90/187	138/188	0.66 (0.55–0.78)
McDonald ⁴⁸	7/29	26/36	0.33 (0.17–0.66)
Total	353/1577	925/1511	0.32 (0.20–0.52)
Preterm birth < 37 wk			
Carey ⁴²	116/953	121/966	0.97 (0.77–1.23)
Hauth ⁴³	110/426	68/190	0.72 (0.56–0.93)
Joesoef ⁴⁴	51/340	46/341	1.11 (0.77–1.61)
Kekki ⁴⁵	9/187	7/188	1.29 (0.49–3.40)
Klebanoff ⁴⁶	31/119	16/113	1.84 (1.07–3.18)
McDonald ⁴⁷	31/429	32/428	0.97 (0.60–1.55)
McGregor ⁴⁹	9/60	5/69	2.07 (0.73–5.84)
Morales ⁵⁰	8/44	16/36	0.41 (0.20–0.85)
Odendaal ⁵¹	42/136	25/133	1.64 (1.06–2.53)
Ugwumadu ⁵²	11/244	28/241	0.39 (0.20–0.76)
Lamont ⁵³	8/208	19/201	0.41 (0.18–0.91)
Total	426/3146	383/2906	0.93 (0.70–1.22)
Preterm birth < 35 wk			
Carey ⁴²	48/953	49/966	0.99 (0.67–1.46)
Preterm birth < 34 wk			
Morales ⁵⁰	2/44	4/36	0.41 (0.08–2.11)
Odendaal ⁵¹	19/136	10/133	1.86 (0.90–3.85)
Vermeulen ⁴⁰	1/11	1/11	1.00 (0.07–14.05)
Total	22/191	15/180	1.17 (0.45–3.08)
Preterm birth < 32 wk			
Carey ⁴²	22/953	29/966	0.77 (0.45–1.33)
Joesoef ⁴⁴	16/340	9/341	1.78 (0.80–3.98)
Ugwumadu ⁵²	3/244	6/241	0.49 (0.12–1.95)
Total	41/1537	44/1548	0.95 (0.49–1.85)
Preterm birth < 28 wk			
Odendaal ⁵¹	8/136	3/133	2.6 (0.71–9.62)
Second-trimester miscarriage			
Ugwumadu ⁵²	2/244	10/241	0.20 (0.04–0.89)
Low birth weight (< 2,500 g)			
Carey ⁴²	103/953	109/966	0.96 (0.74–1.23)
Joesoef ⁴⁴	30/334	23/338	1.32 (0.78–2.22)
McGregor ⁴⁹	8/59	3/69	3.12 (0.87–11.22)
Morales ⁵⁰	6/44	12/36	0.41 (0.17–0.98)
Ugwumadu ⁵²	20/240	23/227	0.82 (0.46–1.46)
Lamont ⁵³	18/208	15/201	1.16 (0.60–2.24)
Total	185/1838	185/1837	1.00 (0.73–1.37)
Very low birth weight (< 1,500 g)			
Carey ⁴²	19/953	26/966	0.74 (0.41–1.33)
Ugwumadu ⁵²	10/240	4/277	2.36 (0.75–7.43)
Lamont ⁵³	3/208	4/201	0.72 (0.16–3.20)
Total	32/1401	34/1394	1.01 (0.49–2.11)
Admission to NICU			
McDonald ⁴⁷	1/429	4/428	0.25 (0.03–2.22)
Ugwumadu ⁵²	18/238	23/228	0.75 (0.42–1.35)
Total	19/667	27/656	0.70 (0.39–1.23)
Perinatal death			
Odendaal ⁵¹	7/136	3/133	2.28 (0.60–8.64)
Ugwumadu ⁵²	1/244	1/241	0.99 (0.06–15.7)
Lamont ⁵³	1/208	3/201	0.32 (0.59–9.29)
Total	9/588	7/575	1.25 (0.40–3.93)
PPROM			
McDonald ⁴⁷	12/429	14/428	0.86 (0.40–1.83)
McGregor ⁴²	9/60	11/68	0.93 (0.41–2.08)
Morales ⁵⁰	2/44	12/36	0.14 (0.03–0.57)
Total	23/553	37/532	0.57 (0.22–1.47)
Peripartum infection			
Kekki ⁴⁵	21/287	33/188	0.64 (0.38–1.06)

CI, confidence interval; NICU, neonatal intensive care unit; PPRM, preterm prelabor rupture of membranes.



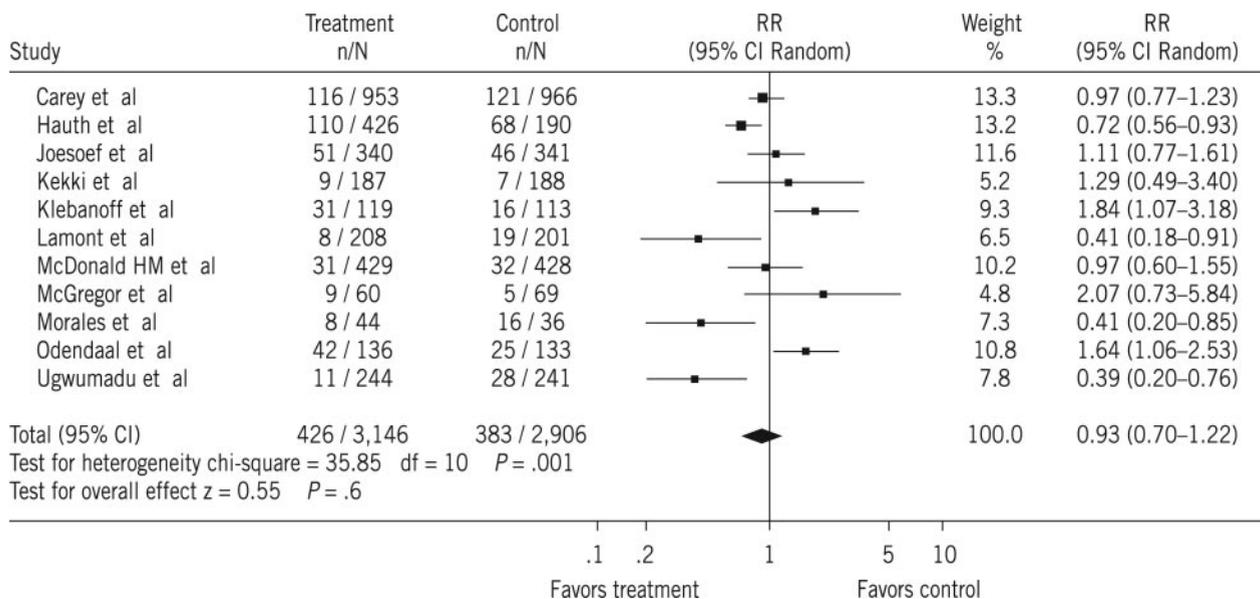


Fig. 1. Effect of antibiotics compared with placebo for women with bacterial vaginosis on the outcome of preterm birth less than 37 weeks.

Okun. Antibiotics for BV and *Trichomonas vaginalis*. *Obstet Gynecol* 2005.

Preterm Birth. Of the 2 studies that assessed the effect of antibiotics for women with *Trichomonas vaginalis*,^{41,46} only the Klebanoff et al⁴⁶ study reported on the rates of preterm birth at less than 37 weeks of gestation. In that study, metronidazole was associated with an increased risk of preterm birth at less than 37 weeks (RR 1.78, 95% CI 1.19–2.66, $P = .005$). There was no significant effect of metronidazole on risk of preterm birth at less than 35 weeks (RR 1.30, 95% CI 0.74–2.29, $P = .40$) or at less than 32 weeks of gestation (RR 1.33, 95% CI 0.63–2.83, $P = .50$).

Preterm Birth At Less Than 37 Weeks Among Subgroups of Women. Among women with *Trichomonas vaginalis* who were at high risk for preterm delivery, Klebanoff et al⁴⁶ reported that metronidazole was associated with a higher risk of preterm birth at less than 37 weeks (RR 1.84, 95% CI 1.07–3.18, $P = .03$). The Ross and Van Middlekoop⁴¹ study did not report on rates of preterm birth but did find that the mean gestational age was not significantly different between women treated with metronidazole compared with placebo ($n = 200$).

Other Outcomes. No effect was found in the 2 studies assessing the effect of metronidazole on the risk of low birth weight ($< 2,500$ g) (RR 1.31, 95% CI 0.92–1.87, $P = .61$).^{41,46} Klebanoff et al⁴⁶ assessed the effect of metronidazole for *Trichomonas vaginalis* in terms of other outcomes. Metronidazole had no effect on the risk of very low birth weight ($< 1,500$ g) (RR 1.42, 95% CI 0.68–2.98, $P = .40$),

admission to a NICU (RR 1.21, 95% CI 0.84–1.75, $P = .30$), neonatal sepsis (RR 1.17, 95% CI 0.74–1.86, $P = .50$), perinatal death (RR 1.28, 95% CI 0.52–3.14, $P = .60$), chorioamnionitis (RR 0.93, 95% CI 0.54–1.59, $P = .80$), or endometritis (RR 1.00, 95% CI 0.46–2.15, $P = 1.0$).

Tests of Heterogeneity

Significant heterogeneity was found when data were pooled from trials for all women with bacterial vaginosis who were treated with any antibiotic compared with no antibiotic for the outcomes of persistent bacterial vaginosis ($P < .001$) and preterm birth at less than 37 weeks of gestation. For the outcome of preterm birth at less than 37 weeks, the heterogeneity persisted among both unselected women ($P < .001$) and women at high risk of preterm birth ($P = .001$). Significant heterogeneity was also found when data were pooled from trials for only women known to have bacterial vaginosis at both randomization and treatment for the outcome of preterm birth at less than 37 weeks ($P < .001$), for all women with bacterial vaginosis treated only with metronidazole ($P = .002$), and for those treated only with clindamycin ($P = .007$).

CONCLUSION

We found that antibiotic treatment for women with bacterial vaginosis consistently reduced the risk of persistent bacterial vaginosis, compared with treatment with



Table 4. Treatment of Bacterial Vaginosis With Antibiotic Compared With No Antibiotics Among Subgroups of Women for the Outcome of Preterm Birth (< 37 wk)

Subgroup/Study	No. With Outcome/Number Randomized		Relative Risk (95% CI)
	Antibiotic Group	Control Group	
High-risk women			
Carey ⁴²	30/101	26/109	1.25 (0.79–1.95)
Hauth ⁴³	47/121	32/56	0.68 (0.49–0.93)
McDonald ⁴⁷	1/17	6/17	0.17 (0.02–1.24)
Morales ⁵⁰	8/44	16/36	0.41 (0.20–0.85)
Odendaal ⁵¹	30/70	12/51	1.82 (1.04–3.20)
Ugwumadu ⁵²	7/36	16/38	0.46 (0.22–0.99)
Total	123/389	108/307	0.75 (0.45–1.24)
Bacterial vaginosis present at randomization			
Carey ⁴²	86/719	93/757	0.97 (0.74–1.28)
Hauth ⁴³	54/172	42/86	0.64 (0.47–0.88)
Joesoef ⁴⁴	51/340	46/341	1.11 (0.77–1.61)
Klebanoff ⁴⁶	31/119	16/113	1.84 (1.07–3.18)
McDonald ⁴⁷	16/242	18/238	0.87 (0.46–1.67)
Morales ⁵⁰	8/44	16/36	0.41 (0.20–0.85)
Odendaal ⁵¹	42/136	25/133	1.64 (1.06–2.53)
Lamont ⁵³	8/208	19/201	0.41 (0.18–0.91)
Total	296/1980	275/1905	0.91 (0.66–1.26)
Treatment with metronidazole			
Carey ⁴²	116/953	121/966	0.97 (0.77–1.23)
Klebanoff ⁴⁶	31/119	16/113	1.84 (1.07–3.18)
McDonald ⁴⁷	31/429	32/428	0.97 (0.60–1.55)
Morales ⁵⁰	8/44	16/36	0.41 (0.20–0.85)
Odendaal ⁵¹	42/136	25/133	1.64 (1.06–2.53)
Total	228/1681	210/1676	1.08 (0.73–1.59)
Treatment with clindamycin			
Joesoef ⁴⁴	51/340	46/341	1.11 (0.77–1.61)
Kekki ⁴⁵	9/187	7/188	1.29 (0.49–3.40)
McGregor ⁴⁹	9/60	5/69	2.07 (0.73–5.84)
Ugwumadu ⁵²	11/244	28/241	0.39 (0.20–0.76)
Lamont ⁵³	8/208	19/201	0.41 (0.18–0.91)
Total	88/1039	105/1040	0.82 (0.45–1.50)

CI, confidence interval.

placebo or no treatment. However, we did not find that antibiotic treatment with either metronidazole or clindamycin reduced the risk of preterm birth at less than 37 weeks, either among all pregnant women with bacterial vaginosis or among any subgroup examined, including those women at high risk of preterm birth. We found no significant reduction in risk of other adverse perinatal outcomes with antibiotic treatment for women with bacterial vaginosis. We believe these findings are valid because the review selected for all high-quality trials that were published as full reports before December 31, 2003.

There have been 3 recently published systematic reviews on antibiotic treatment of bacterial vaginosis, however, that have disagreed with these conclusions.^{11–13} Guise et al¹¹ included 7 trials, all of which were included in our analysis.^{40,42–44,47,49,50} However, 7 studies in our analysis were not included in the review by Guise.^{41,45,46,48,51,52,53} Four of the studies we included were published after the Guise

review was undertaken,^{45,51,52,53} 1 study reported on eradication of bacterial vaginosis only,⁴⁸ and the remaining 2 reported principally on the outcomes of treatment in women with *Trichomonas vaginalis* rather than bacterial vaginosis.^{41,46}

The review by Leitch et al¹² included 10 trials,^{37, 40,42–45,47,49,50,55} two of which we excluded.^{37,55} One of these studied patients in preterm labor,⁵⁵ which was one of our exclusion criteria, and another included data from a duplicate publication.³⁷ Leitch did not include 6 studies that we included.^{41,46,48,51–53} Two of these reported outcomes in women with *Trichomonas vaginalis*.^{41,46} One reported on the primary outcome of eradication of bacterial vaginosis.⁴⁸ Three studies were published^{51–53} after the Leitch review was undertaken.

The most recent Cochrane review included 10 trials (Kekki M, Kurki T, Kurkinen-Raty M, Pelkonen J, Paavonen J. Recurrent bacterial vaginosis in pregnancy



predisposes to infectious morbidity: a double-blind, placebo-controlled multicenter intervention trial with vaginal clindamycin [abstract]. *Int J Gynecol Obstet* 1999;67 suppl 2:S42; Porter K, Rambo D, Jazayeri A, Jazayeri M, Prien S. Prospective randomized trial of once versus twice a day metronidazole-vaginal in obstetrical population identified with bacterial vaginosis [abstract]. *Am J Obstet Gynecol* 2001;184:S166,^{18,40,42-44,47,50,51} 7 of which were included in our analysis.^{40,42-44,47,50,51} Three trials included in the Cochrane review were excluded in our review for the following reasons: one had an excessive dropout rate,¹⁸ one was the abstract (Kekki et al, 1999) of a subsequently published trial,⁴⁵ and one was published in abstract form only (Porter et al, 2001). This latter trial did not include a placebo group but compared once daily with twice daily metronidazole. The 7 studies in our analysis not included in the Cochrane review included 2 studies of women with *Trichomonas vaginalis*,^{41,46} the full trial⁴⁵ of one of their included abstracts (Kekki et al, 1999), 1 study reporting on the outcome of eradication of bacterial vaginosis only,⁴⁸ one study that they stated is "awaiting assessment,"⁴⁹ and 2 studies published after this review was undertaken.^{52,53}

All 3 reviews agree that there is no demonstrated benefit from antibiotic treatment of women with bacterial vaginosis who are not at high risk of preterm birth. However, all 3 suggest that there is potential benefit from screening and treatment of high-risk women. Guise et al¹¹ based this conclusion on pooled data from 3 trials (n = 305)^{43,47,50} demonstrating a reduced incidence of preterm birth at less than 37 weeks, as well as pooled data from two of these studies (n = 128)^{47,50} demonstrating a reduced incidence of preterm premature rupture of the membranes and low birth weight. They propose that screening and treatment of a "more selected" high-risk group (previous preterm delivery and bacterial vaginosis) may reduce the incidence of preterm birth. Leitch et al¹² also propose treatment of high-risk women with an oral preparation for longer duration, based on those studies that demonstrate benefit.^{43,47,50} Finally, McDonald et al (Cochrane review)¹³ conclude similarly that screening and treating high-risk women may lower the incidence of the more important outcomes of premature rupture of the membranes and low birth weight, again based on the studies of McDonald and Morales.^{47,50}

Because our review is more current and we were unable to demonstrate any benefit to antibiotic treatment, even among various subgroups of women, we believe there is inadequate evidence to justify a policy of screening and antibiotic treatment of high-risk women with bacterial vaginosis to reduce the risk of preterm birth. Our review of antibiotic treatment of bacterial

vaginosis includes 2 potentially important recent trials: those of Ugwumadu et al (using oral clindamycin for 5 days)⁵² and Lamont et al (using vaginal clindamycin for 3 days)⁵³ (combined n = 894), which demonstrate a reduced incidence of preterm birth at less than 37 weeks in a general population of pregnant women. Both of these trials treated women earlier than many of the previously published trials. Thus, it is perhaps earlier treatment of bacterial vaginosis, and not necessarily a given preparation, such as the addition of erythromycin⁴³ or treatment of a longer duration,⁵⁰ that alters birth outcomes in both low- and high-risk pregnant women.

We restricted our review to studies that randomized women in the second or third trimester of pregnancy because that is the conventional time to consider antibiotic treatment for bacterial vaginosis and *Trichomonas vaginalis*. However, it is possible that initiation of treatment in the first trimester of pregnancy may have a higher likelihood of being effective. We are unaware of any randomized controlled trials that have evaluated treatment this early in pregnancy.

With regard to the treatment of asymptomatic *Trichomonas vaginalis*, the data available at this time suggest no benefit to treatment for the prevention of preterm birth. Of significance is the fact that one randomized controlled trial⁴⁶ and a subanalysis of a larger trial³⁹ indicate a harmful effect with metronidazole treatment. Although it is not clear why treatment of *Trichomonas vaginalis* with metronidazole would be harmful, it has been speculated that dying *Trichomonas vaginalis* organisms elicit an inflammatory response or release a virus from the organism that increases the risk of preterm birth.⁴⁶

As with other systematic reviews, the trials included in this meta-analysis are limited by the significant heterogeneity of the studies. Sources of heterogeneity may include differences in the diagnostic criteria used for detecting bacterial vaginosis, differences in the timing and length of treatment, the different antibiotics used, and the differences in background risk profiles of the women enrolled. It is not clear how this heterogeneity affected the results, but we believe that earlier antibiotic treatment for women with bacterial vaginosis deserves further study.

Of importance, there was no evidence that treatment of bacterial vaginosis reduced perinatal or neonatal mortality or serious neonatal morbidity, which are more important outcomes than birth at 37 weeks. Justification for screening and treatment strategies should be based on beneficial effects of these more meaningful clinical outcomes and should include evidence that there are no harmful effects on the mother or fetus/neonate. None of the trials to date have adequately addressed these outcomes.



We conclude that there is no evidence to support screening and antibiotic treatment of pregnant women with bacterial vaginosis in the second or third trimester of pregnancy, neither in the general population nor in high-risk women. However, further randomized controlled trials of antibiotic treatment initiated early in pregnancy for bacterial vaginosis, which are powered to assess clinically important outcomes, are warranted. Finally, there is no evidence to support the treatment of asymptomatic *Trichomonas vaginalis* in pregnancy and some evidence that this treatment may be harmful.

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Address reprint requests to: Dr. Nan Okun, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai Hospital, #3276-700 University Avenue, Toronto, Ontario M5G1X5; e-mail: nokun@mtsinai.on.ca.

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