

Evidence on the Benefits and Harms of Screening and Treating Pregnant Women Who Are Asymptomatic for Bacterial Vaginosis: An Update Review for the U.S. Preventive Services Task Force

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Background: Bacterial vaginosis is the most common lower genital tract syndrome among women of reproductive age. There has been continued debate about the value of screening and treating asymptomatic pregnant women for bacterial vaginosis.

Purpose: To examine new evidence on the benefits and harms of screening and treating bacterial vaginosis in asymptomatic pregnant women.

Data Sources: English-language studies on Ovid MEDLINE (2000 to September 2007) and Cochrane Library databases (through September 2007), reference lists, and expert suggestions.

Study Selection: Screening, treatment, or adverse effect studies with pregnancy outcome data in women who are asymptomatic for bacterial vaginosis.

Data Extraction: Study and patient characteristics, treatment variables, adverse pregnancy outcomes, and internal validity quality criteria from the U.S. Preventive Services Task Force (USPSTF) and Jadad scale were abstracted.

Data Synthesis: 7 new randomized, controlled treatment trials and 2001 report data were combined in a series of meta-analyses to

estimate the pooled effect of treatment on preterm delivery (<37, <34, and <32 weeks); low birthweight; and preterm, premature rupture of membranes.

Limitations: No screening studies that compared a screened population with a nonscreened population were found. Significant heterogeneity was found among the high-risk treatment trials ($P < 0.001$). It is not clear from the detailed description of the studies which factors explain the differences in preterm delivery rates and potentially the association of treatment effect; however, both raise concern for the unintended potential for harm.

Conclusion: No benefit was found in treating women with low- or average-risk pregnancies for asymptomatic bacterial vaginosis. More research is needed to better understand these groups and the conditions under which treatment can be harmful or helpful, and to explore the relevance of bacterial vaginosis to other adverse pregnancy outcomes, such as delivery before 34 weeks.

Ann Intern Med. 2008;148:220-233.

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Bacterial vaginosis is the most common lower genital tract syndrome in women of reproductive age (1). It involves an imbalance in the vaginal bacterial ecosystem, such that hydrogen peroxide-producing lactobacilli are diminished and *Gardnerella vaginalis*, anaerobes, and mycoplasmas are abundant. Symptoms can include vaginal discharge, pruritus, or malodor, although approximately half of women with bacterial vaginosis are asymptomatic (2–4). Once the condition is diagnosed, the microflora imbalance can be altered with a short course of antibiotic therapy; however, recurrence is common. The natural history of

bacterial vaginosis in pregnant women has shown that up to 50% of cases of bacterial vaginosis resolve spontaneously during pregnancy (5, 6). Although several antibiotic treatment regimens have been shown to effectively eradicate bacterial vaginosis in pregnant women (7), the treatments recommended in pregnancy by the Centers for Disease Control and Prevention are oral metronidazole (250 mg 3 times daily for 7 days) or oral clindamycin (300 mg twice daily for 7 days) (8, 9).

Researchers have documented the associations between bacterial vaginosis and adverse pregnancy outcomes, focusing on preterm birth and, more recently, the timing of treatment (4, 10–20). This epidemiologic evidence has been used as a rationale for screening asymptomatic pregnant women. The prevalence of bacterial vaginosis in pregnant women seen in community settings is not well studied. In several large, prospective, longitudinal studies, the rate of bacterial vaginosis has ranged from 9% to 23% (11–13, 21–23). Nearly one quarter of white women in an NHANES (National Health and Nutrition Examination Survey) probability sample had Gram stains consistent with bacterial vaginosis (24). Bacterial vaginosis in pregnancy may be more common among minority women, those of low socioeconomic status, and those who have previously delivered low-birthweight infants (12, 25, 26).

See also:

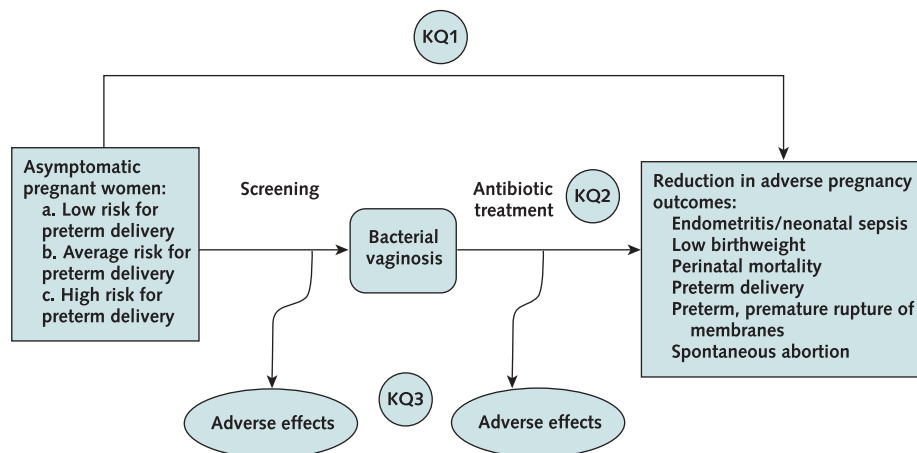
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Appendix
 Appendix Tables
 Appendix Figure
 Conversion of graphics into slides
 Downloadable recommendation summary

Figure 1. Analytic framework and key questions.



Critical key questions:

- Does screening for bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
 - Low risk for preterm delivery?
 - Average risk for preterm delivery?
 - High risk for preterm delivery?
- Does treatment of bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
 - Low risk for preterm delivery?
 - Average risk for preterm delivery?
 - High risk for preterm delivery?
- What adverse effects does the screening and/or treatment of bacterial vaginosis have on pregnancy outcomes?

KQ = key question.

The National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network study found that nearly 50% of pregnant African-American women had bacterial vaginosis (17), similar to the rate found in nonpregnant African American women in NHANES (24).

Recently, concerns have been raised that metronidazole, the most common antibiotic used to treat bacterial vaginosis, may increase preterm births in certain populations. In studies that focus on treatment with metronidazole (often at higher doses for treatment of *Trichomonas vaginalis*), treated pregnant women were up to twice as likely to have a preterm birth as their untreated counterparts (27, 28). The juxtaposition of these data, along with epidemiologic evidence associating bacterial vaginosis with preterm birth, leads to considerable confusion for clinicians and researchers alike. Whether to screen or treat multiple times, when to start, and at what interval during pregnancy are unanswered questions, as bacterial vaginosis may not necessarily persist throughout pregnancy.

This review was conducted for the U.S. Preventive Services Task Force (USPSTF) to update its 2001 recommendations (29–31) by examining the chain of evidence regarding the value of screening for and treating bacterial

vaginosis in reducing adverse pregnancy outcomes for asymptomatic women at low, average, and high risk for preterm delivery.

METHODS

Figure 1 presents the analytic framework and key questions used to guide this updated review.

Data Sources

We searched the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects to identify relevant studies through September 2007 (Appendix Table 1 and Appendix Table 2, available at www.annals.org). In addition, we conducted question-specific searches in Ovid MEDLINE for studies from 1996 to September 2007 and Ovid MEDLINE Database of In-Process and Other Non-Indexed Citations for studies from 2000 to September 2007 to identify otherwise nonindexed studies relevant to any key question. We downloaded and stored captured titles and abstracts in an EndNote database for systematic review and tracking throughout the project. We conducted additional targeted keyword searches and compared the results with the existing database, reviewing

unique citations relating to all key questions for inclusion. We obtained additional articles by comparing reference lists of other systematic reviews, individual studies, editorials, reports, and Web sites and by consulting experts.

Study Selection

We included systematic reviews and individual randomized, controlled trials that evaluated screening, treatment, pregnancy outcomes, or adverse effects for asymptomatic women with bacterial vaginosis. Two investigators independently reviewed captured abstracts by using predefined inclusion and exclusion criteria, and we retrieved any title or abstract that either reviewer marked for inclusion. Two reviewers also independently reviewed full-text papers according to specific criteria. Investigators met to resolve any discrepancies. For a screening trial to be included, we required a comparison of pregnancy outcomes for 2 distinct groups of women: 1 group was screened and treated, and the other was unscreened. We defined asymptomatic patients as those who presented for routine prenatal visits and not specifically for evaluation of vaginal discharge, odor, or itching. Under this definition, asymptomatic patients could include both patients who had no symptoms and those who were unaware of symptoms. We felt this population was most reflective of that encountered in everyday practice. Eligible studies were conducted in settings where pregnant women went for prenatal and obstetric care.

Study participants were categorized as having low, average (general population), or high risk for preterm delivery. Women who had not had a previous preterm delivery or had no other risk factors for preterm delivery (for example, nulliparous women) were considered to be low-risk. The general population, or average-risk, category included all pregnant women presenting to the clinic or study site regardless of risk status. This would include a mix of women at low, average, and high risk for preterm delivery. Women who had a previous preterm delivery due to spontaneous rupture of membranes or spontaneous preterm labor were categorized as high-risk.

We excluded studies of nonpregnant women or those symptomatic for bacterial vaginosis or other infections, as well as studies lacking pregnancy outcomes, animal studies, and non-English-language studies. We reviewed randomized, controlled trials that matched all other criteria except for including multiple infections to ascertain whether bacterial vaginosis-only data were available for any pregnancy outcome, and we excluded studies that only included outcome data for multiple infections.

Data Extraction and Quality Assessment

Two independent reviewers read and extracted data on study design, number of persons who enrolled in and completed the study, setting, patient demographic characteristics, inclusion and exclusion criteria, diagnostic methods, and risk factors. We abstracted all pregnancy outcome data provided. Preterm delivery (that is, the probability of de-

livery before 37 weeks) may be further subdivided into “spontaneous” preterm delivery and “indicated” preterm delivery. Other abstracted outcomes included low birth-weight (defined as <2500 g); preterm, premature rupture of membranes; preterm labor; spontaneous abortion; postpartum endometritis; neonatal sepsis; and intrauterine, neonatal, or perinatal death. We extracted treatment data on reported gestational age at screening and treatment, type of treatment, dose, regimen, administration route, and number of treatment rounds. We documented and summarized all data on adverse effects of treatment, including drug tolerability, study discontinuation related to drug effects, and adverse pregnancy outcomes. We applied a “best-evidence” approach, in which studies with the highest quality and most rigorous designs are emphasized (32).

Two investigators separately evaluated the assessment of relevance and appraisal of internal validity by using the predefined study quality criteria of the USPSTF (33) (Appendix Table 3, available at www.annals.org) and the Jadad (34) rating systems for individual studies (Appendix Table 4 and Appendix Table 5, available at www.annals.org). Raters noted the appropriateness of procedures for patient recruitment and selection, random assignment, blinding, reporting of withdrawals and dropouts, and analyses. Experts in the field suggested that we also abstract study characteristics related to internal validity assessment that are specific to this body of literature. These included patient and provider blinding at second bacterial vaginosis test and second round of treatment, timing and number of dating sonograms obtained before or after random assignment, and types and rates of coinfection. We assigned studies with discrepant quality ratings to a third reviewer and discussed them until we reached consensus. The overall body of evidence for each key question is rated (33) and summarized (35) in a systematic review used by the USPSTF in making their recommendations for preventive services.

Data Synthesis and Analysis

Meta-analysis

When appropriate, we performed a series of meta-analyses that included new trials identified from this search, as well as from studies identified from the previous review, to estimate the effect of treatment on preterm delivery (<37 weeks, <34 weeks, or <32 weeks); low birth-weight; and preterm, premature rupture of membranes. The primary measure of effect of bacterial vaginosis treatment was the absolute risk reduction, which is the difference in proportions of these pregnancy outcomes between the control and treatment group (control minus treatment). We calculated the absolute risk reduction and its SE for each study and used that as the measure of treatment effect. An absolute risk reduction of zero indicated no treatment effect or no difference between the treatment and control groups for adverse pregnancy outcomes. A positive absolute risk reduction favored treatment, indicating

that women receiving treatment for bacterial vaginosis have fewer adverse pregnancy outcomes, whereas a negative absolute risk reduction favored placebo, indicating reduced adverse pregnancy outcomes for those not being treated.

We stratified analyses by risk group (low, average, or high) and pooled them separately to provide a combined estimate of absolute risk reduction and its 95% CI for each group. We used a random-effects model to account for heterogeneity among studies (36, 37). Estimates from a random-effects model would be the same as those from a fixed-effect model if no heterogeneity were found. We used a standard chi-square test to test for heterogeneity and calculated I^2 statistics (38) to quantify the magnitude of heterogeneity. Substantial heterogeneity is evident when P is less than 0.10 and I^2 is greater than 50%. We did not pool absolute risk reductions from the high-risk group studies, because we considered the estimates to be too heterogeneous owing to inconsistent treatment effects.

We performed a sensitivity analysis to address the effect of study quality by excluding trials with a Jadad score of 2 or less. Excluding the trial deemed weak for internal validity did not change combined estimates. We also assessed publication bias by using funnel plots and the Egger linear regression method (39). No publication bias was detected by these methods; however, their interpretation is limited by the small number of trials (40). All analyses were performed by using Stata, version 9.0 (Stata, College Station, Texas).

Outcomes Table on Benefits and Harms

To provide a clinical interpretation of results, we used data derived from the meta-analysis to construct an updated projected outcomes table summarizing estimates of the benefits and harms of screening for bacterial vaginosis in 1000 women at high risk for preterm delivery. These calculations include effect size data from the current meta-analyses and other assumptions about the population of interest (Appendix, available at www.annals.org).

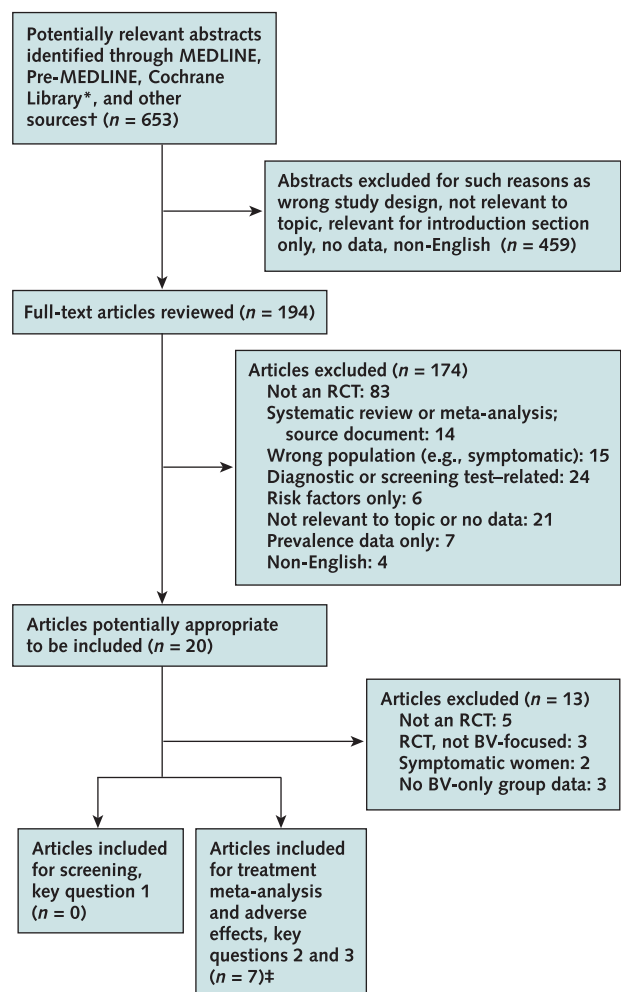
Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency staff and USPSTF members participated in the initial scope of this work and reviewed interim analyses and the final report. We distributed additional reports to content experts for review. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it.

RESULTS

One hundred ninety-four full-text papers were retrieved and screened for eligibility for all key questions. Figure 2 details the search and selection process from the initial title and abstract review, full-text review with reasons for exclusion, and a final count of included studies for

Figure 2. Search and selection of literature for all key questions.



BV = bacterial vaginosis; RCT = randomized, controlled trial. *Cochrane databases include the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. †Other sources include reference lists and expert suggestions. ‡We included 7 additional studies for key question 2 and 2 for key question 3 from the 2001 report in the summary of this evidence.

each key question. Demographic, treatment, and outcome data, as well as quality assessment information on included studies, are found in Appendix Table 6 (available at www.annals.org). Typically, we excluded studies at the paper level because of study design (not a randomized, controlled trial) or sample (such as inclusion of symptomatic pregnant women) or because data on multiple infections with bacterial vaginosis were not separated from data on other infections.

Screening of Pregnant Women Who Are Asymptomatic for Bacterial Vaginosis

We did not identify any studies that compared pregnancy outcomes for women who are asymptomatic for bac-

Figure 3. Study characteristics and absolute risk reduction of delivery before 37 weeks.

	Jadad Score	Completed/Randomized, n/n	Screening Methods & Timing (Week of Gestation)	Baseline Risk*
Low-risk women				
Kurkinen-Räty et al., 2000 (49)	3	101/101	Gram stain (12)	6.0
Kekki et al., 2001 (48)	4	375/375	Gram stain (10 to 17)	3.7
Odendaal et al., 2002 (50)	3	148/150	Gram stain/Amsel (15 to 25)	15.9
<i>All trials combined</i>				
Average-risk women				
McGregor et al., 1994 (55)	3	129/142	Gram stain/Amsel (16 to 27)	7.2
Joeseof et al., 1995 (56)	4	681/745	Gram stain (14 to 26)	13.5
McDonald et al., 1997 (58)	4	480/495	Gram stain (16 to 26)	6.3
Carey et al., 2000 (57)	5	1919/1953	Gram stain (16 to 23)	9.4
Lamont et al., 2003 (53)	5	368/409	Gram stain (13 to 20)	9.8
Guaschino et al., 2003 (51)	2	100/112	Gram stain (14 to 25)	15.7
Kiss et al., 2004 (52)	4	292/297	Gram stain (15 to 20)	5.7
Larsson et al., 2006 (54)	4	819/819	Gram stain (10 to 14)	2.4
<i>Trials (Jadad score ≥3) combined</i>				
<i>All trials combined</i>				
High-risk women				
Morales et al., 1994 (59)	4	80/94	Amsel (13 to 20)	44.4
Hauth et al., 1995 (60)	4	177/177	Amsel (20 to 24)	57.1
McDonald et al., 1997 (58)†	4	34/34	Gram stain (16 to 26)	35.3
Vermeulen and Bruinse, 1999 (61)	4	16/22	Gram stain (20 to 26)	21.2
Carey et al., 2000 (57)†	5	210/213	Gram stain (16 to 23)	22.5
Odendaal et al., 2002 (50)†	3	121/127	Gram stain/Amsel (15 to 26)	23.5

Span = treatment timing spans less than 20 weeks and greater than 20 weeks. *Baseline risk is the percentage of deliveries before 37 weeks in the placebo group. Absolute risk reduction is the difference in probability of delivery before 37 weeks (control minus treatment). †McDonald et al. (58) and Carey et al. (57) performed a high-risk group subanalysis; high-risk group is included in total study population of the average-risk target group. Odendaal et al. (50) included 2 target populations; high-risk and low-risk groups are 2 separate groups.

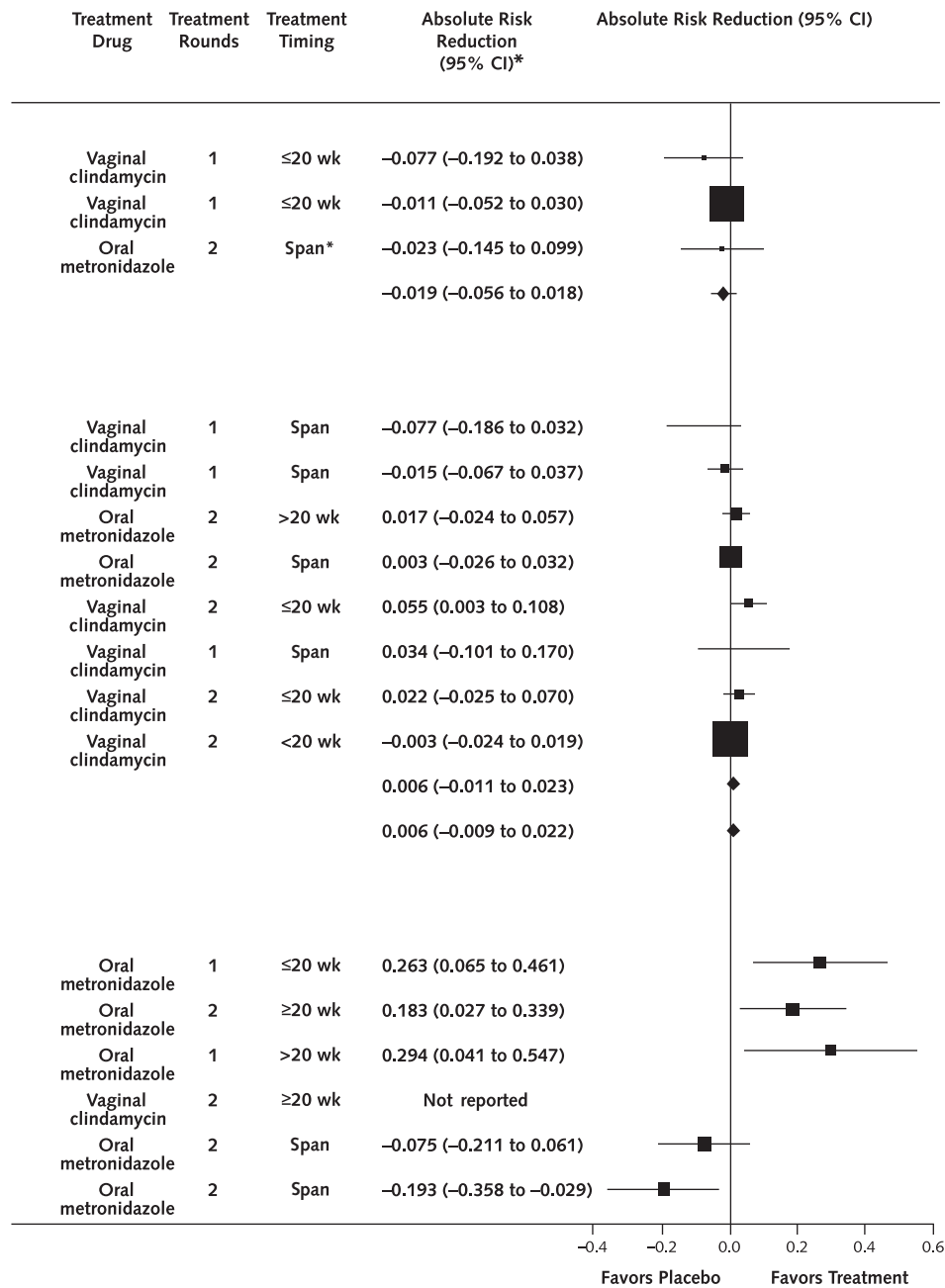
terial vaginosis in a screened population versus a non-screened population.

Treatment of Pregnant Women Who Are Asymptomatic for Bacterial Vaginosis

We found 8 systematic reviews and meta-analyses of bacterial vaginosis treatment in pregnant women published since the 2001 report (7, 41–47). Because the inclusion

and exclusion criteria of the identified systematic reviews and meta-analyses differed from our approach, we decided to use these reviews as source documents only and retrieve relevant, original articles studied in these papers. For example, several reviews assessed studies as good-quality when randomization methods or risk status of the women were unknown, whereas other studies included co-infection groups or symptomatic women.

Figure 3—Continued.



Seven new randomized, controlled trials (48–54) were included in the area of treatment of asymptomatic pregnant women with bacterial vaginosis (Appendix Table 6, available at www.annals.org). All trials treated asymptomatic pregnant women for vaginal syndromes, randomly assigned women to treatment or placebo or no treatment, and provided data for adverse pregnancy outcomes. Studies were stratified by risk (low, average, or high) for preterm delivery. Typically, author definition of risk level matched

that of the reviewers. All studies excluded symptomatic women and women having a multiple pregnancy.

Treatment in Low-Risk Women

The previous review did not identify any low-risk treatment trials, whereas our review identified 3 new randomized, controlled trials (48–50) that provided outcome data for delivery before 37 weeks. Two trials in Finland (48, 49) screened women and treated them with 1 round

of vaginal clindamycin before 17 weeks of gestation, whereas the South African study (50) administered 2 rounds of oral metronidazole later in pregnancy (400 mg twice daily for 2 days at 15 to 25 weeks of gestation). Two of the 3 studies reported co-infection; 1 had a bacteriuria rate of approximately 12%, and showed no differences between the treatment and control groups (50), and 1 had a *Chlamydia trachomatis* rate of 3% and provided no details on distribution relative to the treatment or placebo group (48). Meta-analyses of the 3 trials showed no effect of treatment for delivery before 37 weeks (absolute risk reduction, -0.019 [CI, -0.056 to 0.018]) (Figure 3) and no significant heterogeneity ($P = 0.57$, $I^2 = 0\%$). The South African study was the only study of the 3 to report on delivery before 34 and 28 weeks and intrauterine, neonatal or perinatal death, finding no effect (50). Details regarding clinician knowledge of group allocation were not provided for the South African trial (50), although in another study (49), a high random assignment refusal rate among bacterial vaginosis-positive women was linked to knowledge of diagnostic results. Overall, in reviewing these fair-quality treatment trials, we found no evidence of clinical benefit for treating low-risk pregnant women who are asymptomatic for bacterial vaginosis.

Treatment in the General Population (Average-Risk Women)

We found 4 new treatment trials (51–54) of women at average risk for delivery before 37 weeks that met our inclusion criteria and contributed additional pregnancy outcome data to the original 2001 meta-analysis. These studies are considered average risk because they are general population studies that include a mix of women at low and high risk for delivery before 37 weeks. All new trials administered at least 1 round of treatment with 2% vaginal clindamycin cream; 1 used 1 round only (51), 2 administered the same regimen for subsequent rounds (53, 54), and 1 used oral clindamycin on the second round of treatment (52).

Two population-based treatment trials screened a predominantly white group of asymptomatic pregnant women for bacterial vaginosis in Sweden (54) or multiple infections in Austria (52). In the largest of the trials (54), 819 women in nonhospital clinics received a positive diagnosis for bacterial vaginosis (Gram stain Nugent score, 6 to 10) and then received either vaginal cream or no treatment. No treatment benefit was demonstrated for delivery before 37 weeks (absolute risk reduction, -0.003 [CI, -0.024 to 0.019]) (54). The other infection screening and treatment program included screening for multiple vaginal abnormalities, using a more liberal Gram stain Nugent score (4 to 10) to diagnose bacterial vaginosis in 297 women (52). Although the authors report that the treatment group had significantly fewer births at 37 weeks than those who received placebo, a post hoc analysis by infection type shows that the main effect for treatment was due to candidiasis,

not bacterial vaginosis (absolute risk reduction for data on bacterial vaginosis only, 0.022 [CI, -0.025 to 0.070]).

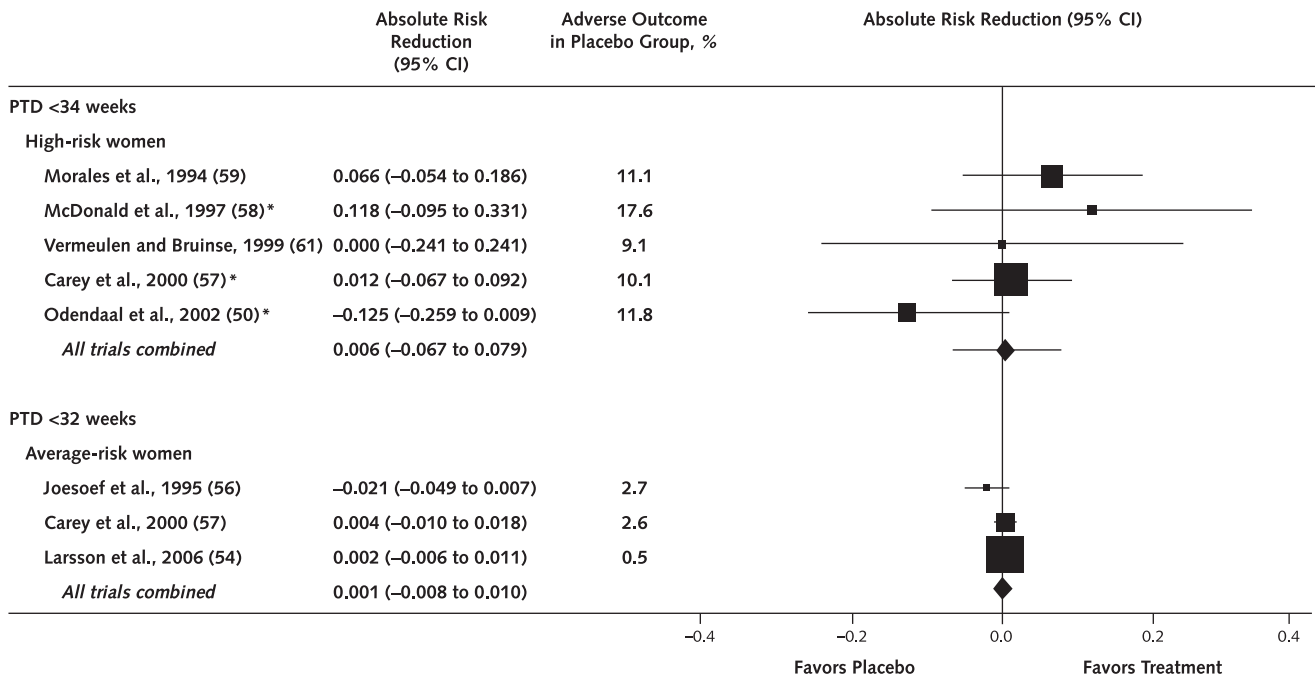
Two additional average-risk bacterial vaginosis treatment trials in the United Kingdom (53) and Italy (51) report differential treatment effects for delivery before 37 weeks in bacterial vaginosis-positive women treated with 2% clindamycin cream. Lamont and colleagues' well-executed hospital clinic trial of 409 women in the United Kingdom at 13 to 20 weeks of gestation reports on a sample comprising 70% white and 15% black women (53). This is the only trial we reviewed in which caregivers and patients were blinded for both rounds of treatment. The women who received treatment were less likely than those who received placebo to deliver before 37 weeks (absolute risk reduction, 0.055 [CI, 0.003 to 0.108]) (53). The average-risk trial from Italy showed no difference in delivery before 37 weeks (absolute risk reduction, 0.034 [CI, -0.101 to 0.170]); however, the study has considerable threats to internal validity (51): Randomization methods were not standard or well described, women and caregivers were not blinded, and concurrent vaginal syndromes were likely.

An updated meta-analysis pooling the new average-risk treatment trials (51–54) with those reviewed in 2001 (55–58) showed no treatment benefit for delivery before 37 weeks (absolute risk reduction, 0.006 [CI, -0.009 to 0.022]), and no significant heterogeneity was detected ($P = 0.36$, $I^2 = 9.6\%$) (Figure 3). Excluding the trial we deemed weak for internal validity (51) did not change combined estimates (Figure 3).

Only 1 new average-risk study explored delivery before 34 weeks and before 32 weeks; no statistically significant results were found (54). When combined with the 2 studies (56, 57) from the previous report, pooled data reveal no treatment effect for delivery before 32 weeks (absolute risk reduction, 0.001 [CI, -0.008 to 0.010]) (Figure 4). Newly identified average-risk trials reported conflicting results for low birthweight (51, 53, 54), and when combined with the studies in the 2001 report (55–58), the pooled estimate for the 7 trials showed no effect of treatment for low birthweight (absolute risk reduction, 0.000 [CI, -0.018 to 0.018]) (Figure 5). Again, no significant heterogeneity was detected ($P = 0.16$; $I^2 = 35\%$), and excluding the trial with compromised internal validity did not change combined estimates. For the outcome of preterm, premature rupture of membranes, 1 new average-risk trial (51) reported a trend toward an adverse effect of treatment; however, it was not statistically significant. When combined with the previously reviewed studies for this outcome (55, 57, 58), pooled results indicated no treatment effect (absolute risk reduction, -0.006 [CI, -0.030 to 0.018]) (Figure 5).

We found several issues related to threats to internal validity that were common to the new average-risk trials, especially where blinding was not apparent or was clearly not achieved (51, 52, 54). Only 1 study (53) reported blinding of care providers and patients throughout the

Figure 4. Absolute risk reduction of delivery before 34 weeks and before 32 weeks.



PTD = preterm delivery. *McDonald et al. (58) and Carey et al. (57) performed a high-risk group subanalysis; high-risk group is included in total study population of the average-risk target group. Odendaal et al. (50) included 2 target populations; high-risk and low-risk groups are 2 separate groups.

study; the investigators administered placebo cream on both rounds of treatment. Lamont and colleagues' study (53) was the only new study to show a treatment effect for any pregnancy outcome (delivery <37 weeks), and pooled results for all outcomes showed no treatment effects. The definition of bacterial vaginosis or abnormal vaginal flora also varied in these studies; however, findings confirm the results of the previous review, showing no pooled treatment effects for any adverse pregnancy outcomes in women who are asymptomatic for bacterial vaginosis in the general population (30). Similar to women at low risk for preterm delivery, the general population seems to lack any clear clinical benefit from screening and treatment for asymptomatic bacterial vaginosis during pregnancy.

Treatment in High-Risk Women

We identified 1 new study (50) since the 2001 report that recruited pregnant women with a history of preterm labor or midtrimester miscarriage who were at high risk for delivery before 37 weeks. In hospital clinics in South Africa, 127 asymptomatic women (86% unmarried; mean age, 27.5 years) at 15 to 26 weeks of gestation who tested positive for bacterial vaginosis were treated with up to 2 rounds of oral metronidazole (400 mg twice daily for 2 days) or 100 mg of vitamin C placebo. Bacterial vaginosis persisted in 30% of the treatment group that was positive for bacterial vaginosis, and an additional 2-day regimen of

metronidazole was provided. Findings reveal a significant adverse effect of treatment on delivery before 37 weeks, indicating that treatment of bacterial vaginosis increased the chance of preterm delivery (absolute risk reduction, -0.193 [CI, -0.358 to -0.029]) (50). We did not pool the results with data from the 2001 report because of substantial heterogeneity among the trials ($P < 0.001$; $I^2 = 82\%$) and inconsistency in the direction of effects. In short, 3 studies in high-risk women showed benefit (58–60), 1 reported significant harm (50), and 1 reported no benefit (57) (Figure 3). See Table 1 for detailed abstraction of these studies.

The new high-risk trial also provides data for the outcome of delivery before 34 weeks, showing no treatment effect (absolute risk reduction, -0.125 [CI, -0.259 to 0.009]) (50). Pooling the outcome data for delivery before 34 weeks from the new trial (50) with the data from the high-risk studies in the 2001 report (57–59, 61) indicates no significant treatment effect (absolute risk reduction, 0.006 [CI, -0.067 to 0.079]) (Figure 4). We found no significant heterogeneity for this outcome ($P = 0.22$; $I^2 = 30\%$). Data for low birthweight and preterm, premature rupture of membranes were not available for the new high-risk study (50). We found statistically significant heterogeneity among the trials identified for the 2001 report for both low birthweight ($P = 0.042$; $I^2 = 69\%$) and preterm, premature rupture of membranes ($P = 0.001$; $I^2 = 86\%$);

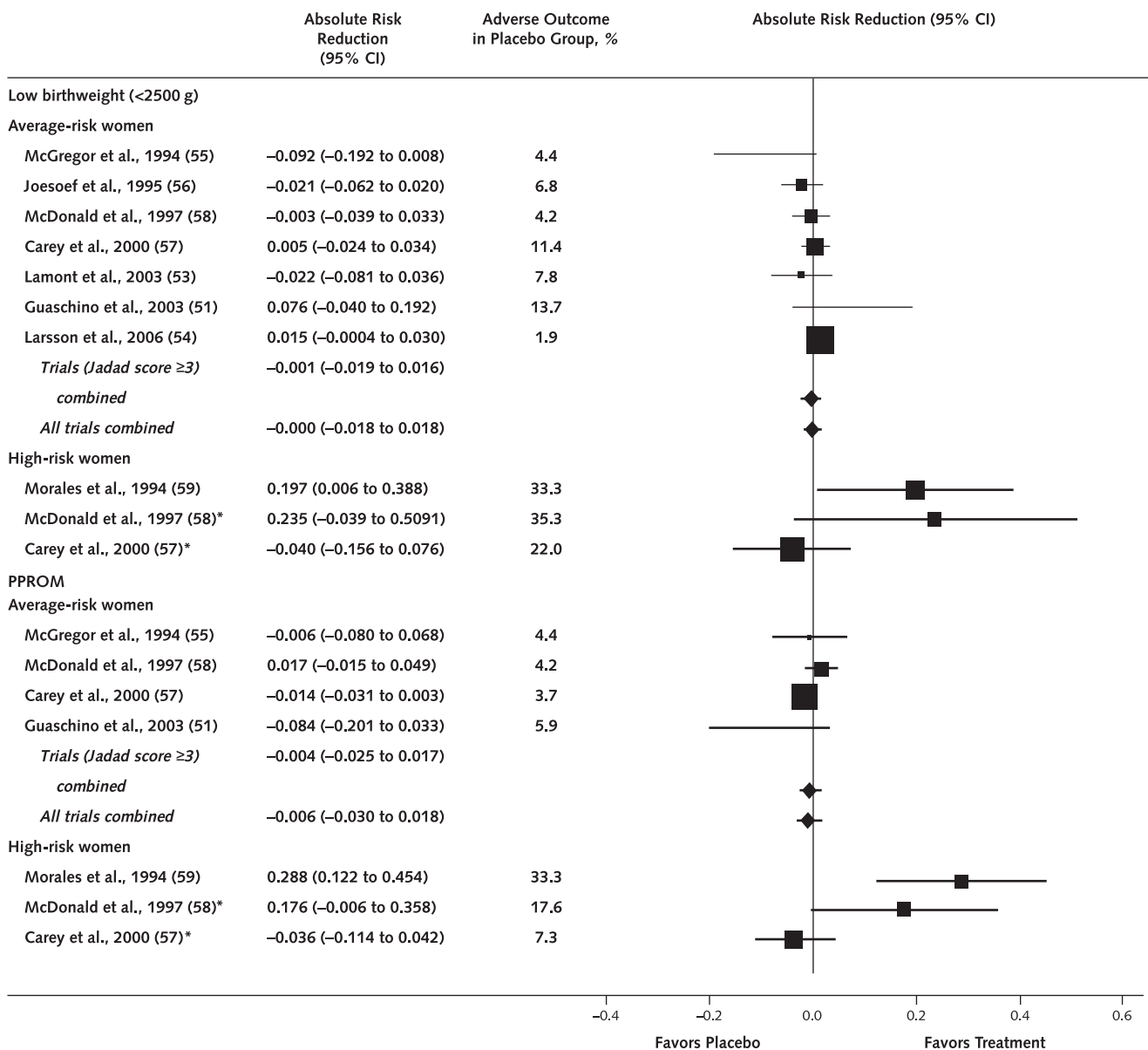
for this reason, and because of the inconsistent harmful and beneficial treatment effects, we did not pool the results for these 2 outcomes (Figure 5).

Summary of Benefits and Harms

We developed an outcomes table (Table 2) to provide an updated clinical interpretation of results for the USPSTF. In looking at the high-risk group, we used data derived from the meta-analysis (50, 57–60) and specific assumptions to approximate the benefits and harms of screening for bacterial vaginosis in 1000 women at high risk for preterm delivery. Estimates are

from studies with a baseline preterm delivery rate of less than 30% (50, 57) for the general high-risk group and greater than 30% (58–60) for the more selected high-risk group. These projections suggest that although a subgroup of high-risk women may benefit from screening and treatment for bacterial vaginosis in pregnancy, a sizeable group would receive either no benefit or may experience harm. The Appendix (available at www.annals.org) provides outcomes table methodology, and the Appendix Figure (available at www.annals.org) shows how the calculations were performed.

Figure 5. Absolute risk reduction of low birthweight and preterm, premature rupture of membranes (PPROM).



*McDonald et al. (58) and Carey et al. (57) performed a high-risk group subanalysis; high-risk group is included in total study population of the average-risk target group.

Table 1. Characteristics of Studies of Women at High Risk for Delivery before 37 Weeks*

Study, Year (Reference)	Country; Setting	Race†	High-Risk Criteria	History of >1 PTD	Treatment Regimen	Rounds, n	Method of Bacterial Vaginosis Diagnosis	Gestational Age at Treatment, wk	Delivery <37 Weeks	
									Untreated Bacterial Vaginosis–Positive Women, %	Treated Bacterial Vaginosis–Positive Women, %
Carey et al., 2000 (57)‡	United States; university, multicenter	White, 14.8%; Black, 69.5%; Hispanic, 15.7%	PTD history	NR	Oral metronidazole, 2 g repeated at 48 h	2	Gram stain	16–24	22.5	30.0
Hauth et al., 1995 (60)	United States; university, Alabama	Black, 73.6%	PTD history or prepregnancy weight <50 kg	NR	Oral metronidazole, 250 mg 3 times/d for 7 d + oral erythromycin, 333 mg 3 times/d for 14 d	2	Amsel criteria	≥20	57.1	38.8
McDonald et al., 1997 (58)‡	Australia; 4 metropolitan area perinatal centers	White, 87.4%; Asian, 8.6%; Aboriginal/Torres Strait Islander, 1%	PTD history	NR	Oral metronidazole, 400 mg 2 times/d for 2 d	2	Gram stain	>20	35.3	5.9
Morales et al., 1994 (59)	United States; university, Baltimore	Black, 47.5%	Penultimate pregnancy, PTD from idiopathic PTL, or PPROM	50% treatment, 39% control	Oral metronidazole, 250 mg 3 times/d for 7 d	1	Amsel criteria	≤20	44.4	18.1
Odendaal et al., 2002 (50)§	South Africa; tertiary academic hospital	NR	PTD history or midtrimester abortion	NR	Oral metronidazole, 400 mg 2 times/d for 2 d	2	Gram stain + Amsel criteria	15–26	23.5	42.9
Vermeulen and Bruinse, 1999 (61)	Netherlands; 12 city hospitals	NR	PTD history, penultimate pregnancy, PPROM	8% treatment, 8% control	Vaginal clindamycin for 7 d	2	Gram stain	≥20	NR	NR

* NR = not reported; PPROM = preterm, premature rupture of membranes; PTD = preterm delivery; PTL = preterm labor.

† Data for race reflect the total population in each study, which may include women without bacterial vaginosis or history of PTD.

‡ Carey et al. (57) and McDonald et al. (58) performed subgroup analyses of high-risk women who were positive for bacterial vaginosis. These women are included in the total population of average-risk women in these respective studies.

§ Odendaal et al. (50) included 2 distinct populations: low-risk women (e.g., primigravidae) and high-risk women (e.g., those with a history of PTD or midtrimester abortion).

|| Includes women both positive and negative for bacterial vaginosis.

In the general high-risk population of 1000 women screened, 238 would receive a correct diagnosis of bacterial vaginosis (assuming 95% accuracy of diagnostic testing), and 190 of these women would successfully complete therapy (assuming 80% adherence). Given these assumptions, we calculate that screening and treating for bacterial vaginosis would result in 24 additional deliveries before 37 weeks (CI, 2 to 45 additional deliveries); 7 additional cases of preterm, premature rupture of membranes (CI, 8 fewer to 22 additional cases); and 7 additional deliveries before 34 weeks (CI, 11 fewer to 25 additional deliveries). Given the data and assumptions for the more selected high-risk group, projections show that screening and treatment would result in an estimated 44 fewer deliveries before 37 weeks (CI, 22 to 64 fewer deliveries); 45 fewer cases of preterm, premature rupture of membranes (CI, 22 to 68 fewer cases);

and 13 fewer cases of delivery before 34 weeks (CI, 33 fewer to 7 additional cases) per 1000 women screened. These findings are consistent with conclusions from the 2001 report.

For the most adverse outcomes, sensitivity analyses show that the accuracy of a reasonable screening test did not change the conclusion of the projected outcomes table. For example, assuming a sensitivity of 80% (instead of 95% as in the above example) for the general high-risk population, screening and treatment results in 20 additional deliveries before 37 weeks (CI, 2 to 38 additional deliveries) and 6 additional cases of preterm, premature rupture of membranes (CI, 7 fewer to 18 additional cases), compared with 24 and 7 additional cases, respectively. Because we assumed a potential increase in delivery before 34 weeks in bacterial vaginosis–negative patients who received treatment, on the basis of data from Hauth and colleagues

(60), the effect of screening on delivery before 34 weeks is moderately sensitive to changes in the accuracy of the screening test. For example, in the more selected high-risk group, we estimate that screening and treatment would result in only 7 fewer cases (CI, 27 fewer to 13 additional cases) of delivery before 34 weeks if the specificity of the screening test for bacterial vaginosis is 80%, compared with 13 fewer cases at a specificity of 95%.

Adverse Effects of Screening or Treatment

We found no studies that directly addressed the adverse effects of screening pregnant women who are asymptomatic for bacterial vaginosis. However, the effects of treatment on women who received an incorrect diagnosis of bacterial vaginosis can provide information on the effect of false-positive test results. None of the 7 new treatment trials included in this review provides data on bacterial vaginosis-negative women receiving treatment. In 2 studies identified in the previous review, bacterial vaginosis-negative women who received antibiotics had more deliveries before 34 weeks than those not given antibiotics; this was statistically significant in 1 study (61) and borderline statistically significant in the other (60). In addition, 1 study reported a statistically significantly greater frequency of neonatal sepsis (61).

One of the 7 treatment trials identified and screened for adverse effects showed an adverse treatment effect for women at high risk for preterm delivery. As noted earlier, asymptomatic pregnant women with a history of preterm labor or midtrimester miscarriage who received metronidazole had a greater chance of preterm delivery than those who received a vitamin C placebo (50). None of the other trials showed statistically significant adverse effects for pregnancy outcomes due to treatment. Adverse effects in the form of treatment tolerability or side effects varied. One study (52) stated that no patients reported adverse reactions to vaginal cream, whereas 3 studies (49, 50, 53) did not report any data on adverse tolerability effects. A trial of vaginal clindamycin reported adverse treatment effects in the form of 3 patient withdrawals due to persistent vulvovaginal itching (54), whereas another trial (48) reported that this side effect occurred with similar frequency in treatment (3.21%) and placebo groups (3.19%).

DISCUSSION

Preterm birth rates have increased in the past decade (62), and strong epidemiologic evidence has suggested an

Table 2. Outcomes Table: Benefits and Harms of Screening 1000 Pregnant Women at High Risk for Bacterial Vaginosis*

Benefit and Relevant Factors	General High-Risk Group (95% CI) [Reference]†	More Selected High-Risk Group (95% CI) [Reference]‡
Assumptions and estimates		
Prevalence of bacterial vaginosis in population	0.25	0.25
Sensitivity of screening test	0.95	0.95
Specificity of screening test	0.95	0.95
Adherence to treatment	0.80	0.80
Effect sizes in patients with bacterial vaginosis§		
Delivery <37 weeks	-0.125 (-0.239 to -0.010) [50, 57]	+0.229 (+0.118 to +0.339) [58-60]
Preterm, premature rupture of membranes	-0.036 (-0.114 to +0.042) [57]	+0.237 (+0.115 to +0.360) [58, 59]
Delivery <34 weeks	-0.033 (-0.126 to +0.060) [50, 57]	+0.079 (-0.026 to +0.183) [58, 59]
Effect sizes in patients without bacterial vaginosis§		
Delivery <37 weeks	0.00	0.00
Preterm premature rupture of membranes	0.00	0.00
Delivery <34 weeks	-0.02	-0.06
Results, n		
Unsuspected bacterial vaginosis	250	250
No bacterial vaginosis	750	750
Correctly diagnosed as having bacterial vaginosis	238	238
Has bacterial vaginosis and has completed therapy	190	190
Incorrectly diagnosed as having bacterial vaginosis	38	38
No bacterial vaginosis and has completed therapy	30	30
Has bacterial vaginosis and missed or did not complete therapy	60	60
Outcomes		
Delivery <37 weeks	-24 (-45 to -2)	+44 (+22 to +64)
Preterm, premature rupture of membranes	-7 (-22 to +8)	+45 (+22 to +68)
Delivery <34 weeks	-7 (-25 to +11)	+13 (-7 to +33)

* The proportion of all patients who meet the criteria for high risk varies with practice setting, patient population, and the criteria used to define high risk. A negative sign (-) indicates a net increase in adverse outcomes (harm), whereas a positive sign (+) indicates a net decrease in adverse outcomes (benefit).

† Preterm delivery baseline risk <30%.

‡ Preterm delivery baseline risk >30%.

§ Probability in control group minus probability in treated group.

|| We used effect size data from high-risk studies where available for specific outcomes.

association between bacterial vaginosis and preterm birth. After decades of research and with heightened awareness of measuring potential adverse effects of medications, evidence is emerging that the drug being used to treat bacterial vaginosis may, at some doses and for some populations, be triggering adverse pregnancy outcomes. At the same time, evidence suggests that inherent differences in populations, such as previous pregnancy complications, gestational age, ethnicity, or co-infection, may also influence which women are helped or harmed by screening and treatment for bacterial vaginosis. New treatment trial data pooled with 2001 report data showed no benefit to screening and treating women who are asymptomatic for bacterial vaginosis if they had a low or average risk for preterm delivery for the outcomes of delivery before 37, 34, or 32 weeks; preterm, premature rupture of membranes; or low birthweight. Results from the studies of women at high risk for preterm delivery are heterogeneous and conflicting. For the outcome of delivery before 37 weeks, 3 of the 5 trials reported a significant treatment benefit, 1 showed significant treatment harm, and 1 showed no benefit (Figure 3). Other reviews have similarly reported no treatment effect for low-risk asymptomatic pregnant women with bacterial vaginosis but suggest a potential but unclear benefit of treatment for some patients at high risk for preterm delivery (7, 44, 45).

Although additional studies of women at high risk for preterm delivery are required to meaningfully explore heterogeneity in a meta-regression, we did examine each study for factors that may explain the variation in treatment response and potentially guide future research (Table 1). One of the clear differences among studies was the variation in baseline preterm delivery rates in the placebo group. It would have been helpful to know the overall preterm birth rate for the clinics in which the studies were conducted because this would allow the greatest opportunity for clinicians to apply results to their own practices. However, because these data were not available for most studies, we documented the preterm delivery rate in the group of bacterial vaginosis–positive women receiving placebo. Studies reporting a baseline risk greater than 30% for delivery before 37 weeks in their bacterial vaginosis–positive placebo groups favored treatment, whereas those with a risk less than 30% favored placebo (Figure 3). Although they were conducted in different countries, the new high-risk trial (50) is most similar to the best-quality high-risk trial identified in the 2001 report (57): Approximately 23% of women positive for bacterial vaginosis in groups receiving placebo delivered before 37 weeks. The study in the 2001 report indicated a trend toward treatment harm for delivery before 37 weeks (57), and the new trial indicated statistically significant harm from treatment for this outcome (50). Although ethnicity is suggested as a potential factor playing a role in both bacterial vaginosis and preterm birth, our data from predominantly minority samples show disparate treatment results (57, 60); reporting of

race data is scarce in other trials. The detailed description of these studies do not clearly indicate which factors may explain the differences in preterm delivery rates or, potentially, the association of treatment effect; however, both raise concerns about the unintended potential for harm.

In addition, the methodological differences among studies could have led to conflicting results. Several methodological challenges arose in synthesizing this body of literature. Only 1 study provided details on blinding procedures throughout the study. Most of the trials did not report whether the women or caregivers continued to be blinded to their group allocation upon re-treatment. The potential to violate intention-to-treat by modifying the estimate of gestational age after random assignment and treatment is another weakness in study design, especially if this estimate were changed differentially in the treatment and control groups: Bias would exist if treatment were associated with a change in the gestational age estimate. However, few studies provided sufficient data on sonography timing to evaluate this factor. In addition, varying definitions of bacterial vaginosis, along with the reporting ambiguity of multiple infection status, make it difficult to meaningfully combine this research. More detailed information on these factors would create greater opportunities to assess both the contributions and potential biases of the studies.

Metronidazole treatment has been associated with adverse pregnancy outcomes in certain subgroups. However, studies to date of bacterial vaginosis in asymptomatic pregnant women have not provided sufficient numbers or details to identify the specific factors playing the most prominent role for harms or benefits. Clinicians need to remain vigilant to the potential harmful effects of bacterial vaginosis treatments, because no screening test is 100% accurate. Researchers are in an uncomfortable position of uncertainty, balancing the ethics of continuing potentially risky investigations with the possibility of substantial benefit. Only when multiple, well-executed studies consistently point to the same subgroups showing benefits or harms does confidence increase that such differences are real (63). More research is needed to better understand these groups and the conditions under which treatment can be harmful or helpful and to explore relevance to other adverse pregnancy outcomes, including preterm delivery before 34 weeks.

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Acknowledgment: The authors thank Andrew Hamilton, MLS, MS, for conducting the literature searches, and USPSTF leads Kimberly Gregory, MD, MPH, Lucy Marion, PhD, RN, and Diana Petitti, MD, MPH, and AHRQ officers Iris Mabry, MD, MPH and Mary Barton, MD, MPP, for their guidance on this project.

Grant Support: This report was conducted by the Oregon Evidence-

based Practice Center under contract to the Agency for Healthcare Research and Quality, Rockville, MD, according to Contract #290-02-0024, Task Order Number 2 for the USPSTF.

Potential Financial Conflicts of Interest: None disclosed.

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APPENDIX: OUTCOMES TABLE METHODOLOGY

As described in the earlier report (29, 30), we performed this computation with 2 populations at high risk for preterm delivery, based on the placebo groups' baseline risk for delivery before 37 weeks. The general high-risk population has a baseline risk of less than 30% for delivery before 37 weeks, whereas the more selected high-risk population has a baseline risk of greater than 30%. In the outcomes table, the case for the general high-risk population incorporates the mean and 95% CIs from 2 high-risk studies in which approximately 23% of the bacterial vaginosis-positive women in the placebo group delivered before 37 weeks (50, 57) for the listed outcomes. The second scenario, for the more selected high-risk population, incorporates the pooled results of the other 3 high-risk studies (58–60), in which the percentage of bacterial vaginosis-positive women in the placebo groups who

delivered before 37 weeks is greater than 30% (see Table 2). The effect sizes of treatment on bacterial vaginosis-positive pregnant women are therefore based on this review.

We assumed the prevalence of unsuspected bacterial vaginosis to be 25%, both screening test sensitivity and specificity to be 95%, and adherence to treatment to be 80%. The prevalence of bacterial vaginosis in asymptomatic pregnant women has ranged from 9% to 23% in several large prospective studies (11–13, 21–33). Because the outcomes table presents estimates based on high-risk women, it is reasonable to assume that the prevalence of bacterial vaginosis is somewhat higher for this group. We see this as a realistic estimate of prevalence in this population, although it is not directly derived from the literature. For sensitivity and specificity, we assumed a high-quality screening test. We performed a sensitivity analysis to assess the influence of the alternative assumptions of lower sensitivity and specificity on the calculated benefits and harms as well.

Appendix Figure 1 (available at www.annals.org) provides an example of the calculations performed for the outcomes table, using the outcome of delivery before 34 weeks in the more selected high-risk population.

Appendix Table 1. Overall Searches

Database	Search Strategy
EBM Reviews—Cochrane Central Register of Controlled Trials	1) vaginosis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
	2) (pregnan\$ or labor or prematur\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
	3) 1 and 2
EBM Reviews—Cochrane Database of Systematic Reviews	1) vaginosis.mp. [mp=title, abstract, full text, keywords, caption text]
	2) (pregnan\$ or labor or prematur\$).mp. [mp=title, abstract, full text, keywords, caption text]
	3) 1 and 2
EBM Reviews—Database of Abstracts of Reviews of Effects	1) vaginosis.mp. [mp=title, full text, keywords]
	2) (pregnan\$ or labor or prematur\$).mp. [mp=title, full text, keywords]
	3) 1 and 2
Pre-Ovid MEDLINE In-Process and Other Nonindexed Citations	1) vaginosis.mp.
	2) (prematu\$ or preterm\$ or (pre adj term) or low birth weight\$ or lbw or (spontaneous\$ adj abort\$)).mp. [mp=title, original title, abstract, name of substance word]
	3) 1 and 2
	4) pregnan\$.mp. [mp=title, original title, abstract, name of substance word]
	5) 1 and 4
	6) 3 or 5
	7) limit 6 to humans [Limit not valid; records were retained]
	8) limit 7 to English language
	9) limit 7 to abstracts
	10) 8 or 9
	11) limit 10 to yr="2000 - 2006"

Appendix Table 2. Specific Searches per Key Question*

Key Question	Search Strategy
1—Screening	<ol style="list-style-type: none"> 1) exp VAGINOSIS, BACTERIAL/di 2) vaginosis.mp. 3) exp Pregnancy Complications, Infectious/di, ep 4) 2 and 3 5) exp PREGNANCY COMPLICATIONS/ or exp PREGNANCY/ 6) 1 and 5 7) exp mass screening/ or screen\$.mp. 8) pregnan\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 9) 7 and 8 10) 2 and 9 11) 4 or 6 or 10 12) limit 11 to yr="2000 - 2006" 13) limit 12 to humans 14) limit 13 to English language 15) limit 13 to abstracts 16) 14 or 15
2—Treatment	<ol style="list-style-type: none"> 1) exp VAGINOSIS, BACTERIAL/dt, th [Drug Therapy, Therapy] 2) vaginosis.mp. 3) exp Pregnancy Complications, Infectious/dt, th, pc 4) 2 and 3 5) exp fetal membranes, premature rupture/dt, th, pc or exp labor, premature/dt, th, pc 6) 2 and 5 7) exp PREGNANCY COMPLICATIONS/ or exp PREGNANCY/ 8) 1 and 7 9) 4 or 6 or 8 10) limit 9 to yr="2000 - 2006" 11) limit 10 to humans 12) limit 11 to English language 13) limit 11 to abstracts 14) 12 or 13
3—Adverse effects	<ol style="list-style-type: none"> 1) exp pregnancy/ or exp pregnancy complications/ or exp Embryonic Structures/de 2) ((adverse\$ adj5 effect\$) or harm or harmed or harms or harming or defect\$ or malform\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 3) clindamycin.mp. or exp Clindamycin 4) metronidazole.mp. or exp Metronidazole 5) (ae or to or po).fs. 6) 2 or 5 7) 3 or 4 8) 1 and 6 and 7 9) vaginosis.mp. 10) exp Anti-Bacterial Agents 11) exp Bacterial Infections/dh, dt, th [Diet Therapy, Drug Therapy, Therapy] 12) 10 or 11 13) 9 and 12 14) 1 and 6 and 13 15) 8 or 14 16) limit 15 to (humans and English language)

* Database: Ovid MEDLINE.

Appendix Table 3. U.S. Preventive Services Task Force Quality Rating Criteria

RCTs and cohort studies

Criteria

Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)

Important differential loss to follow-up or overall high loss to follow-up

Measurements equal, reliable, and valid (includes masking of outcome assessment)

Clear definition of interventions

Important outcomes considered

Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria

Good: Studies will be graded “good” if they meet all criteria—comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis

Fair: Studies will be graded “fair” if any or all of the following problems occur without the important limitations noted in the “poor” category below:

Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for

Poor: Studies will be graded “poor” if any of the following major limitations exists: Groups assembled initially are not close to being comparable or are not maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention

Diagnostic accuracy studies

Criteria

Screening test relevant, available for primary care, adequately described

Study uses a credible reference standard, performed regardless of test results

Reference standard interpreted independently of screening test

Handles indeterminate results in a reasonable manner

Spectrum of patients included in study

Sample size

Administration of reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100) and a “medium” spectrum of patients

Poor: Has important limitation, such as use of inappropriate reference standard; improperly administered screening test; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients

Case-control studies

Criteria

Accurate ascertainment of cases

Nonbiased selection of case and control participants with exclusion criteria applied equally to both

Response rate

Diagnostic testing procedures applied equally to each group

Measurement of exposure accurate and applied equally to each group

Appropriate attention to potential confounding variables

Definition of ratings based on above criteria

Good: Appropriate ascertainment of case participants and nonbiased selection of case and control participants; exclusion criteria applied equally to case and control participants; response rate equal to or greater than 80%; diagnostic procedures and measurements accurate and applied equally to case and control participants; and appropriate attention to confounding variables

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias, but with response rate less than 80% or attention to some but not all important confounding variables

Poor: Major selection or diagnostic work-up biases, response rates less than 50%, or inattention to confounding variables

RCT = randomized, controlled trial.

Appendix Table 4. Jadad Scale Criteria

A numerical score from 0 to 5 is assigned as a rough measure of study design and reporting quality (0 being weakest and 5 being strongest). This number is based on the validated scale developed by Jadad et al. (34).

This calculation does not account for all study elements that may be used to assess quality (other aspects of study design and reporting are addressed in tables and text).

A Jadad score is calculated using the 7 items in **Appendix Table 5**. The first 5 items are indications of good quality, and each counts as 1 point toward an overall quality score. (Give a score of 1 for each yes and 0 for each no. There are no in-between marks.)

The final 2 items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Randomization: A method to generate the sequence of randomization will be regarded as appropriate if each study participant was allowed to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Inappropriate methods of allocation are date of birth, date of admission, hospital numbers, or alternation.

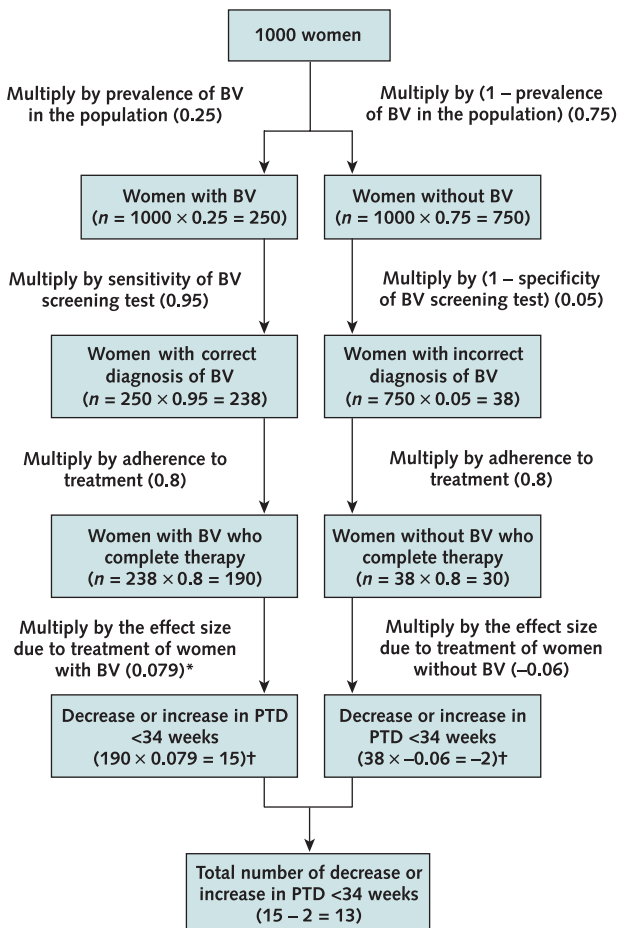
Double-blinding: A study must be regarded as double-blind if the word "double-blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if, in the absence of such a statement, the use of active placebos, identical placebos, or dummies is mentioned.

Withdrawals and dropouts: Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given 0 points.

Appendix Table 5. Jadad Score Calculation

Item	Score
Was the study described as randomized (this includes such words as "randomly," "random," and "randomization")?	0/1
Was the method used to generate the sequence of randomization described and was it appropriate (e.g., table of random numbers, computer-generated)?	0/1
Was the study described as double-blind?	0/1
Was the method of double-blinding described and was it appropriate (e.g., identical placebo, active placebo, dummy)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct 1 point if the method used to generate the sequence of randomization was described but was inappropriate (e.g., patients were allocated alternately or according to date of birth or hospital number).	0/−1
Deduct 1 point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Appendix Figure. Illustration of calculation in Table 2, using the outcome of delivery before 34 weeks in the more selective high-risk group.



BV = bacterial vaginosis; PTD = preterm delivery. *To calculate the confidence limits for the increase or decrease in adverse outcome, plug in the confidence limits of effect size here. †A negative sign (–) indicates a net increase in adverse outcomes (harm), and a positive sign (+) indicates a net decrease in adverse outcomes (benefit).