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Screening and Treatment for Bacterial Vaginosis in Pregnancy: Systematic Review to Update the 2001 U.S. Preventive Services Task Force Recommendation

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Structured Abstract

Objectives: Bacterial vaginosis (BV) is the most common lower genital tract syndrome among women of reproductive age. This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2001 recommendation on screening and treatment for bacterial vaginosis in pregnancy. This update report will focus on three critical key questions related to screening, treatment, and adverse effects of screening and/or treatment on pregnancy outcomes in women asymptomatic for bacterial vaginosis at low, average, and high risk for preterm delivery. The previous review and recommendations can be downloaded at http://www.ahrq.gov/clinic/uspstf/uspsbvag.htm.

Data Sources: Searches were conducted in the Cochrane Central Database of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects through the second quarter of 2006. We also searched Ovid MEDLINE and the Ovid MEDLINE Database of In-Process and Other Non-Indexed Citations from January 2000 to July 2006.

Review Methods: All captured citations and retrieved papers were independently rated for inclusion in the study by two reviewers, using established inclusion/exclusion criteria related to three critical key questions. Studies of screening or treatment included randomized controlled trials that evaluated screening and/or treatment pregnancy outcomes and/or adverse effects for asymptomatic women with bacterial vaginosis (BV). Participants included pregnant women at low, average, or high risk for preterm delivery. Eligible studies were available in the English language. Studies were also sought by reference lists of related reviews, studies, editorials, reports, websites, and by consulting experts. The USPSTF quality rating system and the Jadad scale (RCTs) were used to rate study quality.

Data Synthesis and Analysis: Data on study characteristics, treatment variables, and adverse pregnancy outcomes were abstracted. For each study, we calculated the absolute risk reduction (ARR), and analysis was stratified by risk group (low, average, or high risk). When data allowed, we performed a series of meta-analyses (using new and 2001 report data) to estimate the pooled effect of treatment on preterm delivery (<37 weeks, <34 weeks, or <32 weeks), on low birth weight (LBW), and on preterm premature rupture of membranes (PPROM).

Screening Results: No studies comparing a screened population with a non-screened population were found.

Treatment Results: Seven new randomized controlled trials were found in the area of treatment of asymptomatic pregnant women with BV since the previous report was published in 2001. Meta-analysis of trials showed no treatment effects at any risk level for preterm delivery for preterm delivery (PTD) <37 weeks, PTD < 34 weeks, PTD < 32 weeks, PPROM, or LBW (<2500g). We did not pool the PTD < 37 weeks, LBW, or PPROM outcome data from high-risk patients due to significant heterogeneity among the trials and inconsistency in the direction of treatment effect. For

PTD <37 weeks, three of the five trials reported a significant treatment benefit, while one showed significant treatment harm, and the other showed no benefit.

Conclusion: We found no evidence to support screening or treating low-risk pregnant women asymptomatic for BV. Similarly, we found no benefit to screening for and treating BV in the general population of pregnant women who are asymptomatic for BV. (This finding confirms results of the prior review.) Studies of screening and treating women at high risk for preterm delivery conflict on the degree of benefit.

Future Research: Future studies are needed to prospectively evaluate the benefit of screening and treating asymptomatic BV in women at highest risk for PTD (that is,, greater than a 3-fold increased risk). Conducting such studies well requires standardization of screening timing, treatment regimen (drug, dose, frequency) and detailed measures and reporting of risk factors and outcomes.

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I. INTRODUCTION

Preface

Systematic evidence reviews serve as the basis for U.S. Preventive Services Task Force (USPSTF) recommendations on new clinical prevention topics. The USPSTF tailors the scope of these reviews to each topic.

The USPSTF last reviewed screening for bacterial vaginosis (BV) in 2001. Using the review prepared by Guise and colleagues[1, 2] the USPSTF decided to recommend against routinely screening average-risk asymptomatic pregnant women for bacterial vaginosis (BV) with a **D recommendation.** The USPSTF also concluded that the evidence is insufficient to recommend for or against routinely screening high-risk pregnant women for BV with an **I recommendation.** Clinical considerations for populations at high risk were also provided.[3]

The USPSTF made the update of the BV topic a priority for 2006. Gaps in evidence evident from the prior recommendation included information that would make it possible to characterize the patients most likely to benefit from screening, evidence about the optimum timing of screening and treatment, information to determine the effect of treatment on pregnancy outcomes, the fact that the screening methods used in research do not reflect those used in practice, and the fact that the findings of studies in U.S. health clinics are not generalizable to community-based practices.

Condition Definition

Bacterial vaginosis (BV) is the most common lower genital tract syndrome among women of reproductive age.[4] 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 include vaginal discharge, pruritus, or malodor; however, approximately half of women with BV are asymptomatic.[5-7] Once diagnosed, the microflora imbalance can be altered with a short course of antibiotic therapy.

Prevalence and Burden of Disease

For two decades now, researchers have documented the associations between BV and adverse pregnancy outcomes focusing on preterm birth and timing of treatment.[7-16] This epidemiologic evidence has been used as a rationale for screening asymptomatic pregnant women for BV.

Most data on the prevalence of infection come from academic medical centers or public hospitals. In several large prospective, longitudinal studies performed in these settings, the prevalence of BV has ranged from 9 to 23%.[9-11, 17-19] The prevalence of BV in pregnant women seen in community settings is not well studied. BV in pregnancy is more common among African-American women,

women of low socioeconomic status, and those who have previously delivered low-birth weight infants.[10, 20]

The recently completed National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network study found that forty-five percent of the African American women in this sample had BV.[15] In a secondary analysis of 4 prospective studies in Denver, rates of BV and other vaginal infections were significantly higher among Black women than among non-Hispanic white or Asian comparators (39.8 vs. 24.6, respectively).[20] A predominantly Caucasian sample of 4,429 pregnant women presenting for routine prenatal care in non-hospital-based clinics in Vienna had a 8.6% rate of BV.[21]

The natural history of BV in pregnant women has shown that up to 50% of BV cases resolve spontaneously during pregnancy.[22-24] Whether or not to screen and/or treat multiple times, and when to start and at what interval during pregnancy, are still unanswered questions, as BV may not necessarily persist throughout pregnancy.[22]

Current Clinical Practice

Diagnosis

BV is diagnosed using Amsel's clinical criteria or Gram stain. Using Amsel's criteria, the clinical diagnosis is made by fulfilling three out of four criteria: (1) vaginal pH > 4.7, (2) the presence of clue cells on wet mount, (3) thin homogeneous discharge, and (4) amine "fishy odor" when potassium hydroxide is added to the discharge.[5] Two different Gram stain scoring systems, Nugent's[25] and Spiegel's[26] have been developed and compared with Amsel's clinical criteria. Gram stain of vaginal discharge may be a more reliable means of diagnosing BV, and it offers the added ability of quantifying and classifying bacterial load.[1] For these reasons, Gram stain has been the primary means used to diagnose BV in epidemiologic and treatment studies, with Nugent's criteria accepted as the preferred method.[1]

Gram stain is less commonly used in clinical practice because of the need for laboratory facilities and the consequent delay in receiving diagnostic results. Because most data on pregnancy outcomes and their association with BV and improvement with BV treatment are based on studies that used Gram stain as their diagnostic criteria, a question remains as to whether research findings for pregnancy outcomes can be directly translated into practice.[1]

Accuracy of Diagnostic Methods in Clinical Versus Research Settings (Subsidiary Question)

Authors of the previous review noted that the preferred diagnostic test would be one that predicts pregnancy outcomes with the most accuracy. The current review identified two publications that

evaluated various diagnostic tests in predicting preterm birth: a meta-analysis[27] and a secondary analysis[28] of 12,041 women who were screened for the BV Trial,[29] but not randomized to either metronidazole or placebo therapy.

The secondary analysis of women screened but not randomized for the BV Trial assessed whether there were threshold values of vaginal pH and Gram stain scores in early pregnancy that were linked with subsequent preterm birth.[27] The meta-analysis included 11 observational studies that tested for BV using Nugent's criteria for Gram staining (7 studies, n=13,729), Spiegel's criteria for Gram staining (2 studies, n=927), or clinical criteria that included microscopy (2 studies, n=3067). The pooled results showed no differences between the various tests in their accuracy for predicting preterm birth. The meta-analysis was limited by the small number of studies that were combined for each test.[27]

The analysis of women screened but not randomized for the BV Trial assessed threshold vaginal pH and Gram stain scores in early pregnancy (8-22 weeks) that were predictive of subsequent preterm birth. Pregnancy outcomes were available for 12,041 of 21,554 women with vaginal pH determined at screening, and for 6,838 of 12,010 women who had both vaginal pH $\geq$ 4.5 and a Gram stain result. The study found that women with vaginal pH $\geq$ 5.0 had a significantly increased incidence of subsequent spontaneous preterm delivery (PTD) at <37, <35, and <32 weeks, compared with women with vaginal pH < 5.0 ($p<0.0001$). Women with vaginal pH >=4.5 and Gram stain scores of 9 to 10 had a higher risk of spontaneous PTD < 37 weeks compared with women having a Gram stain score of 8 or less. The proportion of women with PTD <37 weeks was similar among women with vaginal pH >=5.0 (12.4% of 2759) and women with vaginal pH >=4.5 and Gram score of 9 to 10 (12.6% of 1664).[28] These results suggest that a higher-risk population may be defined using vaginal pH >=5, or the combination of vaginal pH >=4.5 with Gram score of 9 to 10. The analysis, however, did not directly compare vaginal pH with Gram stain alone in the prediction of spontaneous PTD.

One study[30] found that using any 2 of 3 clinical criteria (viz. ph >4.5, whiff test positive, and clue cells positive) had a sensitivity of 56%, specificity of 96%, positive predictive value of 83%, and negative predictive value of 85%, compared with Gram stain diagnosis of BV as the standard. False positive rates of the individual clinical components versus Gram stain-based diagnosis were 48% for pH >4.5, 29% for positive whiff test, and 25% for clue cells present on wet smear. The proportion of false positives for the clinical diagnosis overall was 4%, calculated as 1 minus specificity. (The study reported a false positive rate of 17%, apparently calculated as 1 minus positive predictive value. The conventional method for calculating the false positive rate, however, is 1 minus specificity). The authors of the study attributed these findings to the "subjective nature of the clinical test."[30] Another study that similarly defined BV on the basis of 2 of 3 clinical signs (ph > 4.5, presence of clue cells, positive whiff test) showed improved sensitivity over Amsel criteria that additionally included appearance of vaginal secretions. (36.3% vs. 63.6%, using Gram stain as the reference). The false positive rate for the modified criteria was 2%.[31]

None of the studies identified by the literature search on the diagnostic accuracy of clinical criteria documented whether clinicians routinely implement all of part of Amsel's clinical criteria in practice. The extent to which research findings would apply to the practice setting therefore remains unclear. Two studies suggested that the presence of clue cells as the sole diagnostic criterion has a

false positive rate (i.e., 1 minus specificity) of 6%, and a false negative rate (i.e., 1 minus sensitivity) of 41%[31] to 50%.[30]

Treatment

The previous systematic review describes in detail the therapies used for treating BV, recommended dosages during pregnancy. and cure rates.[1] Oral metronidazole and oral clindamycin, as well as vaginal metronidazole gel or clindamycin cream, are used to treat BV. The Centers for Disease Control and Prevention (CDC) reports that cure rates are 78% to 84% in gynecologic patients taking oral metronidazole 500 mg twice a day for 7 days, 82% for clindamycin 2% vaginal cream once daily for 7 days, and 75% for metronidazole gel twice a day for 5 days.[32] A systematic review of randomized controlled trials of BV treatment in pregnancy found treatments to be comparable in their effectiveness at eradicating BV.[33] In pregnancy, oral metronidazole and oral clindamycin are the recommended regimens, with metronidazole gel as an alternative. Citing adverse pregnancy outcomes, the CDC does not recommend using vaginal clindamycin cream during pregnancy. The CDC-recommended treatment for BV in pregnancy is 250 mg oral metronidazole 3 times a day for 7 days 70–4. This lower dosage is recommended to minimize exposure to the fetus.[32]

Systematic Reviews in the Field

We reviewed 8 systematic reviews and meta-analyses of BV treatment in pregnant women identified by the searches and published since the 2001 report.[34-41] Because the inclusion and exclusion criteria of these systematic reviews and meta-analyses differed from this review, we decided to use these reviews as source documents, and retrieve relevant, original articles from these papers. For instance, a number of reviews included studies where randomization methods were unknown or where details on how risk groups were categorized were not provided. We chose to update this work with the same methods utilized by the 2001 report team.

The majority of the reviews[34-36, 38] report no treatment effect for BV positive, asymptomatic pregnant women, while suggesting that there is a benefit of treatment for patients at high risk for preterm delivery.[34, 38, 39]

Recommendations from Other Groups

The Centers for Disease Control (CDC),[42] American College of Obstetricians & Gynecologists (ACOG),[43] Cochrane Pregnancy and Childbirth Group,[34] British Association for Sexual Health and HIV (BASHH)/Clinical Effectiveness Group (CEG),[44] National Institutes of Health (NIH),[45] American Academy of Family Physicians (AAFP),[46] and National Institute of Clinical Excellence (NICE)[47] make similar screening and/or treatment recommendations for pregnant women with BV. All recommend against routine screening for BV in asymptomatic, pregnant women. Regarding women at high risk for preterm delivery, the CDC, ACOG, AAFP, and BASHH state that there may

be a group of high-risk women for whom screening and treatment may be beneficial, consistent with prior USPSTF recommendations. In contrast, the NIH recommends screening all women with prior spontaneous preterm delivery. The CDC does not recommend the use of vaginal cream.

Focused Systematic Review Aims

This report will be used by the USPSTF to update the 2001 recommendation[3] on screening for bacterial vaginosis in pregnancy. The format and methods of the previous systematic evidence review developed previously by Guise and colleagues[1] will be used to guide this update. The lead investigator on this 2001 report served as a consultant for this update. The previous review can be viewed at http://www.ahrq.gov/clinic/uspstf/uspsbvag.htm.

Analytic Framework and Questions

An analytic framework was developed to outline issues and focus the literature search (Figure 1). The analytic framework begins with a population of pregnant women asymptomatic for BV who are at low risk, average risk, or high risk for preterm delivery. Typically, women were considered to be at low risk if they had not had a previous preterm delivery, or other risk factors for preterm delivery (often these were nulliparous women). The average risk category includes women in the general population of pregnant women presenting to the clinic or study site, which would include a mix of low, average, and high risk women. Women were considered to be of high risk if they had a previous preterm delivery due to spontaneous rupture of membranes or spontaneous preterm labor. For the most part, these definitions were used consistently by authors in the papers we reviewed. Asymptomatic patients were defined as those who presented for routine prenatal visits and not for evaluation specifically of vaginal discharge, odor, or itching. Under this definition, asymptomatic could include both patients who were without symptoms and those who were unaware of symptoms. This population was felt to be most reflective of that encountered in everyday practice.

Preterm delivery (PTD), the probability of delivery before term (37 weeks), was the primary outcome measure considered in the literature search. Preterm delivery may be further subdivided into “spontaneous” preterm delivery and “indicated” preterm delivery. Spontaneous preterm delivery arises mainly from preterm premature rupture of membranes or preterm labor. Other outcomes considered were low birth weight (LBW) (<2500 grams), preterm premature rupture of membranes (PPROM), preterm labor, spontaneous abortion, postpartum endometritis, neonatal sepsis, and neonatal death.

Specifically, this systematic review updates the evidence from 2001 to the present for the following

questions:

Critical Key Questions

1. Does screening for bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at low risk, average, or high risk for preterm delivery?
2. Does treatment of bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at low, average, or high risk for preterm delivery?
3. What adverse effects does the screening and/or treatment of bacterial vaginosis have on pregnancy outcomes?

Subsidiary Question

Also stated as important to explore is the accuracy of the diagnostic methods used to diagnose bacterial vaginosis in the clinical setting as compared with research methods. This question is described in the introduction section of this report.

II. METHODS

Literature Search and Strategy

We conducted literature searches relevant to our critical key questions (Appendix A). All citations and articles were managed in an electronic database (Endnote®). Searches were conducted in the Cochrane Central Database of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects through the 2nd quarter of 2006 to identify studies relevant to the critical key questions. The Ovid MEDLINE Database of In-Process and Other Non-Indexed Citations was searched from January 2000 to July 2006 to identify otherwise non-indexed studies relevant to any critical key question. In addition, key question specific searches were conducted for key questions 1, 2, and 3 in Ovid MEDLINE from January 1996 to July 2006.

We identified 8 systematic reviews[34-41] and used those systematic reviews as sources of relevant randomized controlled trials for this review. In addition to the list obtained through database searching, articles were also obtained by comparing reference lists of reviews, studies, editorials, reports, and websites; and by consulting experts.

Inclusion and Exclusion Criteria

Investigators dually reviewed abstracts identified by the searches and papers identified as described above for potential relevance to all critical key questions, and determined eligibility by applying inclusion and exclusion criteria (Appendix B). Eligible studies related to the screening and treatment key questions were conducted in settings where pregnant women went for prenatal and obstetric care. These settings included both university-based and non-university-based obstetric and hospital clinics. Systematic reviews and individual randomized controlled trials that evaluated screening and/or treatment pregnancy outcomes and/or adverse effects for asymptomatic women with bacterial vaginosis (BV) were reviewed. Participants included pregnant women at low, average, or high risk for preterm delivery. Eligible studies were in the English language and conducted in the U.S. or a developed country.[48] Studies of non-pregnant women, studies lacking pregnancy outcomes, studies of poor quality, and animal studies were excluded (Appendix C). Studies where excluded if the focus of the study was multiple infections and data was not available for the BV group only. A "best evidence" approach was applied, in which studies with the highest quality and most rigorous design are emphasized.[49]

Critical Appraisal

Two reviewers independently rated the quality of studies using design-specific criteria developed by the USPSTF[50] and Jadad[51] **(**Appendix D). Reviews were not excluded based on quality, as searching for individual trials within these reviews was our priority. The overall rating for each individual

study is a combination of internal and external validity scores. When reviewers disagreed, a final rating was reached through consensus. Good or fair quality individual randomized controlled trials are emphasized in this report.

Size of Literature Reviewed

A total of 570 unique citations (Appendix E) were identified from the literature searches, the previous report, reference lists, and through expert referrals. Two hundred nine abstracts were reviewed to identify literature showing direct evidence of screening related to reduced adverse pregnancy outcomes, of which none met the inclusion criteria (KQ 1). Two hundred thirteen abstracts were reviewed to identify literature showing evidence that treatment reduces adverse pregnancy outcomes, of which 7 randomized controlled trials, and 8 systematic reviews that were used for source documents, met the inclusion criteria (KQ 2). Seventy-four abstracts were reviewed to identify literature showing evidence whether there are adverse effects associated with screening and/or treatment of bacterial vaginosis on pregnancy outcomes, of which 9 met the inclusion criteria (KQ 3). One hundred seventy-eight additional abstracts from keyword searches were reviewed for applicability to any of the questions, and then combined with the appropriate questions. (Seven treatment trials and 5 adverse effects studies from the 2001 report will be synthesized with the new evidence).

Data Synthesis

Data from the full text of the original articles and systematic reviews were abstracted to evidence tables. The data included study, year, setting, patient demographics, inclusion/exclusion criteria, and risk status. Pregnancy outcome data included completed weeks of gestation at delivery, preterm premature rupture of membranes (PPROM), neonatal death, and other pregnancy outcomes if provided. Abstracted treatment data included gestational age (in weeks) at screening/treatment, type of treatment, dose, regimen, administration route, number of treatment rounds, and adverse effects. Data on the percentage of adverse pregnancy outcomes in the BV-positive treatment group and percentage of adverse pregnancy outcomes in the BV-positive placebo group were also abstracted. Summary tables with specific information were then developed for use of the team in evidence synthesis and by the statistician to provide further analysis of the data.

Statistical Analysis

We performed a series of meta-analyses that included trials located for this review and the previous review to estimate the effect of treatment on preterm delivery (<37 weeks, <34 weeks, or <32 weeks), on LBW, and on PPROM. The primary measure of effect of BV treatment was the difference in proportions of pregnancy outcomes between the control and treatment group, the absolute risk reduction (ARR) [Control – Treatment]. A zero would indicate no treatment effect, or no differences between the treatment and control groups for adverse pregnancy outcomes. A

negative ARR favors placebo, where reduced adverse pregnancy outcomes are evident for those not being treated. A positive ARR favors treatment where those being given the treatment show less adverse pregnancy outcomes. For each study, the absolute risk reduction (ARR), and its standard error was calculated and used as the measure for the effect of treatment. Analysis was stratified by risk group (low, average or high risk group) and studies were pooled when appropriate to provide a combined estimate of ARR and its 95% confidence intervals (CI). If there was evidence of heterogeneity among trials at a significance level of $P = .10$ based on the standard chi-square test for heterogeneity, we used a random effects model.[54] To address the effect of quality of trials, we performed a sensitivity analysis by excluding poor quality trials with a Jadad score ≤ 2.

We also assessed publication bias by using funnel plots and Egger's linear regression method.[55] No publication bias was detected by these methods, however, their interpretation is limited by the small numbers of trials for each therapy.[56] All analyses were performed using Stata version 9.0 (StataCorp LP, College Station, Tex).

Summary of Benefits and Harms

To provide a clinical interpretation of the results, estimates derived from the meta-analysis and systematic reviews of studies of screening for BV were used to construct an updated balance sheet that summarizes the benefits and harms of screening for BV in 1,000 high-risk women.[57]

External Review Process

The USPSTF appointed the author of the previous systematic review to advise the Oregon Evidence-based Practice Center in formulating and reporting this update. An additional set of outside experts (see Appendix F) provided advice on a draft version of the evidence synthesis, presented at the July 13-14, 2006 Task Force Meeting. The feedback was fully incorporated into the final report.

III. RESULTS

Key Question 1. Screening of Pregnant Women Asymptomatic for BV and Pregnancy Outcomes

We did not find any studies that compared pregnancy outcomes for women asymptomatic for BV in a screened population and a non-screened population.

Key Question 2. Treatment of Pregnant Women Asymptomatic for BV and Pregnancy Outcomes

a. Low-risk Women

The previous review did not identify any low risk groups. Three fair or good quality randomized controlled treatment trials[22, 58, 59] with data for low risk (without a history of PTD) pregnant women are included in this review (Appendix G - Evidence Table). Two trials[22, 59] treated women with one round of vaginal clindamycin, while the third used two rounds of oral metronidazole.[58] Pooled estimate in the low-risk studies showed no effect of treatment for PTD <37 weeks (ARR -0.019, 95% CI -0.056 to 0.018) (Tables 1 and 2). We did not find significant heterogeneity in the low risk trials. Confidence intervals for the individual studies and pooled results all cross zero with the absolute risk reduction (ARR) negative (Figure 2).

Data for pooling results were not available for other adverse pregnancy outcomes for the low-risk group.

b. General Population or Average-risk Women

Two good quality population-based BV screening and treatment trials of asymptotic pregnant women[21, 60] were published since the 2001 report. Both screened a large asymptomatic sample of pregnant women in a general practice population for vaginal syndromes, randomized women to either treatment or placebo, and provided outcome data on adverse pregnancy outcomes. Additionally, one good[61] and one poor quality[62] randomized controlled treatment trial of average-risk pregnant women asymptomatic for BV are included since the last review (Appendix G - Evidence Table).

Pre-term delivery. A good quality population-based infection screening program trial[21] included twenty-five non-hospital-based clinics in Vienna Austria. Four thousand four hundred twenty-nine pregnant women were screened for multiple vaginal abnormalities, including BV (using gram stain), Candida, and Trichomonas vaginalis syndromes. This population was considered to be at average risk for a preterm delivery, as it included low-, average-, and high-risk women. (Appendix G - Evidence Table). BV was diagnosed using Nugent's criteria. Two hundred ninety-seven women were randomized to either intervention or placebo. Treatment consisted of clindamycin 2% vaginal cream for 6 days, and those women with persistent or recurrent BV at second screen were treated with oral clindamycin 300mg twice daily for 7 days. Authors report that the treatment group had significantly fewer preterm births at 37 weeks when compared to placebo. Using outcome data by infection type from this publication, this result does not remain significant for the BV group (ARR 0.022, 95% CI -0.025 to 0.070). In a post hoc analysis, it appears that the Candidiasis infection group provides the main effect for treatment in this study.

In another recent good quality, large population-based screening program, 9,025 asymptomatic pregnant women were screened in non-hospital based clinics in Sweden for BV.[60] BV was diagnosed using Nugent's criteria and the 819 women positive for BV were randomized to either placebo or treatment with clindamycin 2% vaginal cream (7 days). Persistent BV at second screen was treated again with this regimen. No benefit of treatment was found for PTD <37 weeks (ARR -0.003, 95% CI -0.024 to 0.019).[60]

Two additional average-risk BV treatment trials published since 2001 reported mixed results. Lamont's good quality study of 409 women in the United Kingdom given 2% clindamycin cream for 7 days compared to placebo showed a small benefit for preterm delivery <37 weeks in the treatment group (ARR 0.055, 95% CI 0.003 to 0.108).[61] A poor quality study of 112 Italian women given the same regimen and dosage, without a second round of treatment, showed no benefit for treatment for PTD <37 weeks (ARR 0.034 ,95% CI -0.101 to 0.170).[62]

An updated meta-analysis pooling the PTD <37 weeks outcome for both the new average-risk treatment trials[21, 60-62] with those reviewed in 2001,[29, 63-65] showed no treatment benefit for PTD <37 weeks (ARR 0.006, 95% CI, -0.009 to 0.022). We did not find significant heterogeneity in the average risk trials (Figure 2).

No new studies for the general population looked at the outcome of PTD <34 weeks.

For PTD <32 weeks, one new average risk trial reporting this outcome showed no significant result.[60] When combined with the two studies[29, 64] from the previous report providing PTD <32 week data, no treatment effect was found (ARR 0.001, 95% CI, -0.008 to 0.010) (Figure 3). We did not find significant heterogeneity in the average risk trials.

Other adverse pregnancy outcomes. Newly reviewed trials reporting a low birth weight outcome[60, 61, 62] showed no treatment effects. When combined with the 2001 report's average-risk population studies for this outcome,[29, 63-65] the pooled estimate for the seven trials also showed no effect of treatment (ARR -0.000, 95% CI, -0.018 to 0.018) (Figure 4). Significant heterogeneity was not found in these trials.

For the PPROM outcome, one new average-risk trial[62] reported no treatment effects. When combined with the previously reviewed studies for this outcome,[29, 63, 65] pooled result indicated no treatment effect (ARR -0.006, 95% CI-0.030 to 0.018) (Figure 4).

c. High-risk Women

We found one recently published study of high-risk pregnant women, defined as a history of PTD in a prior pregnancy. This was a fair quality study of 127 women in hospital clinics in South Africa treated with oral metronidazole (400 mg BID 2 days)[58] (Appendix G - Evidence Table).

Pre-term delivery. The high risk women in the new study showed a significant adverse effect of treatment for PTD <37 weeks (ARR -0.193, 95%CI, -0.358 to -0.029)[58] (Figure 2).

Trial data for the PTD <37 weeks outcome from high-risk patients for both the newly reviewed trial[58] and those reviewed in 2001,[29, 65-67] showed significant heterogeneity (Q=22.432, df=4, P <0.0001), and treatment effects were not consistent in directions therefore were not pooled. Three[65-67] of the five trials saw a significant treatment benefit, while one showed significant treatment harm,[58] and the other showed no benefit[29] (Figure 2**).**

Pooling the PTD <34 weeks high risk population outcome for the new trial,[58] plus the 2001 report studies[29, 58, 65, 67, 68] indicates no significant treatment effect (ARR 0.006, 95% CI -0.067 to 0.079).(Figure 3). There was no significant heterogeneity seen for this outcome (p=0.219).

Other adverse pregnancy outcomes. Data for low birth weight and PPROM were not available for the new high-risk study.[58]

2001 high-risk trial data[29, 65, 67] for LBW and PPROM outcomes were not pooled as and treatment effects were not consistent in directions and significant heterogeneity among the trials was detected (Q=6.362, df=2, P = 0.042 and Q=14.399, df=2, P = 0.001, respectively) (Figure 4).

Detailed study data on high-risk studies. A detailed summary of high-risk study characteristics, including aspects of treatment, setting, race, and the study population, is provided in Table 3. Further review of these data may provide additional information and a better understanding of the heterogeneity in this data, in order to enhance clinicians' decisionmaking for treatment choices.

Summary

Seven new randomized controlled trials were found in the area of treatment of asymptomatic pregnant women with BV since the previous report was published in 2001. When new and 2001

report trial data were pooled, meta-analysis showed there were no treatment effects for women asymptomatic for BV at any risk level (Figures 2-4). We did not pool the PTD <37 weeks, LBW or PPROM outcome data from high-risk patients due to significant heterogeneity among the trials and inconsistency in the direction of treatment effect. For PTD <37 weeks, three of the five trials reported a significant treatment benefit, while one showed significant treatment harm, and the other showed no benefit.

Key Question 3. What Adverse Effects Does the Screening and/or Treatment of Bacterial Vaginosis Have on Pregnancy Outcomes?

Adverse Effects of Screening

No studies addressed the adverse effects of screening.

Adverse Effects of Treatment

Adverse outcomes in BV-negative women. In two studies identified in the previous review, significantly more adverse pregnancy outcomes occurred among BV-negative women who received treatment for BV compared with BV-negative women who were not given antibiotics.[66, 68] Preterm delivery prior to 34 weeks occurred more frequently in the BV-negative group in both studies, and one study also reported a greater frequency of neonatal sepsis.[68] The current review identified one study conducted in fetal-fibronectin-positive (FFN-positive) women, in which 446 BV-negative women were randomized to receive metronidazole (250mg TID, 10 days) plus erythromycin (250mg QID, 10 days) or placebo.[69] Among FFN-positive/BV-negative women in this study, spontaneous PTD <37 weeks occurred more frequently in the treatment group compared with placebo (13.1% vs. 10.6%), but the increase was not statistically significant.

Prenatal Exposure to Metronidazole. The previous review reported that two meta-analyses of metronidazole treatment of case-control and cohort studies found no evidence for teratogenesis, with summary ORs of 1.02 and 1.08 (95%CI 0.98-1.27).[1] Recent observational studies similarly found no association between metronidazole and congenital abnormalities.[70-72]

A retrospective cohort study determined cancer incidence in children who were exposed prenatally to metronidazole.[73] The cohort included children younger than 5 born to women enrolled in Tennessee Medicaid during pregnancy, and the analysis adjusted for maternal age, race, marital status, education, county of residence, and whether the child was first born. The study found no increase in total cancer risk, but did observe an elevated risk for neuroblastomas (RR 2.6, 95%CI 0.89-1.82) that, though not statistically significant, may warrant further study.

All randomized controlled treatment trials discussed in KQ2, published post 2000, were reviewed for any adverse treatment effects data. Three of the trials[58, 59, 61] did not provide any data on adverse treatment effects beyond pregnancy outcomes previously highlighted in the KQ2 section. One trial[21] stated that none of the patients reported adverse reactions to treatment. Another trial reported an adverse fracture event, however, study group status could not be determined.[62]

Tolerability. One study provided data on treatment tolerability.[22] In a trial of vaginal clindamycin, vulvovaginal itching occurred with similar frequency in the treatment group (3.21%) as in the placebo group (3.19%).[22]

A recent trial with oral clindamycin (N=485)[74] included women with abnormal intermediate flora (Nugent score 4-6), as well as those diagnosed with Bacterial Vaginosis. Discontinuation of therapy due to side effects occurred more frequently with clindamycin than with placebo, but the difference was not statistically significant (7% v. 3%, p=0.10). Reports of side effects in this study included gastrointestinal upset (10 placebo, 5 clindamycin), rashes (1 placebo, 1 clindamycin), vulvovaginal candidiasis (1 placebo, 1 clindamycin), throat irritation (1 placebo) and headaches (1 placebo, 4 clindamycin).

The tolerability of oral and vaginal metronidazole formulations was assessed in a study of cervical cytokine response in BV-positive pregnant women.[75] The study reported that subjects tolerated the medications well, with high levels of compliance for both formulations of the drug.

Summary

No studies addressed the adverse effects of screening. The effects of treatment on women incorrectly diagnosed to have BV have been indirectly studied. The previous review describes two studies of BV-negative women who received treatment for BV compared with BV-negative women who were not given antibiotics, and found an increased frequency of PTD <34 weeks in the BV-negative group in both studies. A new study found that among FFN-positive/BV-negative women, there was a non-significant increase in spontaneous PTD <37 weeks in the treatment versus placebo group.

Recent observational studies confirm findings from the 2001 report of no association between metronidazole and congenital abnormalities. A retrospective cohort study of children exposed prenatally to metronidazole showed mixed results for cancer outcomes and may warrant further study. A number of new treatment studies reported on medication tolerability. There were no statistically significant differences between oral and vaginal clindamycin treatment and control groups, and oral and vaginal metronidazole showed high compliance and tolerability.

IV. DISCUSSION

Screening

No studies compared pregnancy outcomes for pregnant women asymptomatic for BV in a screened population verses a non-screened population. Two good quality, large population-based screening and treatment trials in Sweden and Austria provide some data on screening and treatment and are discussed in the treatment section.

Treatment

Low- and Average-risk Women

The three BV treatment studies of women at low risk for a preterm delivery <37 weeks were not available for the 2001 report. The meta-analysis conducted for this review found no benefit to treating low-risk women for BV in reducing preterm deliveries.

Two good population-based screening and treatment trials in Sweden and Austria did not find a benefit for preterm delivery <37 weeks, while the Swedish trial found a small benefit for low birth weight. The meta-analysis for the average-risk women are consistent with the prior review in finding no benefit to screening and treating BV in the general population.[1]

High-risk Women

Studies of screening and treating women asymptomatic for BV at high risk for preterm delivery show conflicting results for treatment benefit. It should be noted, however, that the 3 studies that reported significant treatment benefits also had placebo groups (BV positive) with a percentage of preterm delivery at 37 weeks greater than 30 percent. In contrast, the two high-risk studies that showed either significant treatment harm or no treatment effect had a lower percentage placebo baseline risk for PTD <37 weeks, 24% and 22.5% respectively. More research is needed to better understand this observation, and to explore relevance to other adverse pregnancy outcomes including preterm deliveries less than 34 weeks.

Summary of Benefits and Harms

As noted in the 2001 report, the finding of benefit in some high-risk studies suggests that there may be a subgroup of high-risk women who benefit from screening and treatment for BV in pregnancy. The draft balance sheet in Table 4 updates the work of 2001 and summarizes our estimates of the

consequences of screening for BV in 1000 patients from the general high-risk population and 1000 from a more selected high-risk population incorporating the new high-risk data. The base case for the general high-risk population incorporates the mean and 95% CIs from the two high-risk studies with approximately 23 percent of their placebo, BV-positive women experiencing a PTD <37 weeks[29, 58] for the listed outcomes. The second scenario incorporates the pooled results of the other three high-risk studies,[65-67] where the percentage of BV-positive women in their placebo group experiencing a PTD <37 weeks is >30 percent (Table 3). For this work, we also assumed that the screening test has a sensitivity of 95% and specificity of 95%, the prevalence of unsuspected BV is 25%, and that adherence to treatment is 80%.

In the general high-risk population, of 1000 women screened, 238 are correctly diagnosed to have BV, and 190 of these complete therapy. With screening and treatment there would be 24 additional preterm deliveries before 37 weeks (95% CI=2 to 45 additional cases), 7 additional cases of preterm premature rupture of membranes (95% CI=8 fewer to 22 additional cases), and 2 fewer preterm deliveries before 34 weeks (95% CI=17 fewer to 13 additional cases). These results are similar to the 2001 report, however, the confidence interval for the PTD <37 weeks outcome does not include zero (no effect), indicating a significant result.

In the more selected high-risk group, results remain consistent with the 2001 report. Screening and treatment results in 44 fewer preterm deliveries before 37 weeks (95% CI=22 to 64), 45 fewer cases of preterm premature rupture of membranes (95% CI=22 to 68), and 11 fewer cases (95% CI=29 fewer to 8 additional cases) of preterm delivery before 34 weeks per 1000 women screened.

Because we assumed a potential increase in preterm delivery before 34 weeks in BV-negative patients that received BV treatment (based on Hauth 1995[66]), the effect of screening on preterm delivery less than 34 weeks is moderately sensitive to changes in the accuracy of the screening test. In the more selected high-risk group, for example, screening and treatment result in an increase in preterm delivery before 34 weeks if the specificity of the screening test for BV is below 80% (not shown).

Adverse Effects of Screening and Treatment

There are no studies that directly address the issue of adverse effects of screening.

The effects of treatment on women incorrectly diagnosed to have BV have been indirectly studied. The previous review describes two studies of BV-negative women who received treatment for BV compared with BV-negative women who were not given antibiotics and found an increased frequency of PTD <34 weeks in the BV-negative group in both studies. A new study found that among FFN-positive/BV-negative women, there was a non-significant increase in spontaneous PTD <37 weeks in the treatment versus placebo group.

Recent observational studies confirm findings from the 2001 report of no association between metronidazole and congenital abnormalities. In terms of medication tolerability, there were no

statistically significant differences between oral and vaginal clindamycin treatment and control groups, and oral and vaginal metronidazole showed high compliance and tolerability.

Overall Evidence

Table 5 provides a summary for the level of evidence found for the critical key questions for this review.

Future Research

Future studies are needed to prospectively evaluate the benefit of screening and treating asymptomatic BV in women at highest risk for adverse pregnancy outcomes (e.g., greater than a 3-fold increased risk for PTD). Also, there remains substantial controversy regarding specific drugs chosen for BV treatment. Studies reported a wide range of treatment regimens, route, dose, duration, and treatment timing. The three studies with the highest preterm birth rates all reported significant treatment benefits, having used oral therapy (metronidazole). Agreement on treatment course would speed the field in moving forward to identifying the appropriate group and therapy for benefit.

The sample size for future studies needs to be calculated with better knowledge of the characteristics of the proposed study population, including characteristics such as race, the prevalence of BV, the preterm delivery rate (<37 as wells as <34 or <32 weeks), and the proportion of women with a prior spontaneous PTD. Studies thus far are relatively under-powered to study significant benefits for adverse pregnancy outcomes other than PTD <37 weeks. Perhaps a large health system or multi-site university-based research clinic or network collaboration might create this opportunity.

A report reviewer also suggested that future research in this area needs to specify the estimated reduction in relative risk expected in the trial. These assumptions have in general not appeared in publications of results of randomized trials. Perhaps these assumptions should be published so that future studies can benefit.

The importance of accurate screening to avoid treating BV-negative women needs attention. No studies assess what methods clinicians actually use to diagnose BV in practice, and whether clinicians routinely implement all of Amsel's clinical criteria before making a treatment decision. If minimal clinical criteria (e.g., microscopy and whiff test only) are routinely being used to diagnose BV in primary care or obstetric clinics, pregnant and non-pregnant women without BV may be inappropriately treated. Is it possible that more BV-negative women are given treatment in general practice settings, as opposed to research settings, where strict clinical criteria or lab tests are required to make treatment decisions? Again, the extent to which diagnosis and treatment in the research field applies to the clinical setting still remains unclear.

In typical ‘real-world’ clinical settings, the Amsel and Gram stain techniques for screening asymptomatic women for BV are not practical. Many clinicians often rely on two of Amsel’s four criteria for diagnosis of BV (discharge and clue cells). In addition, Gram stains are subject to quality control mechanisms that are part of routine laboratory quality control protocols, conditions that the typical clinician using a microscope for a wet mount would not be subject to. The study of false-positive wet mount readings and clinician judgment and treatment preferences linked to pregnancy outcomes would provide more information in this field.

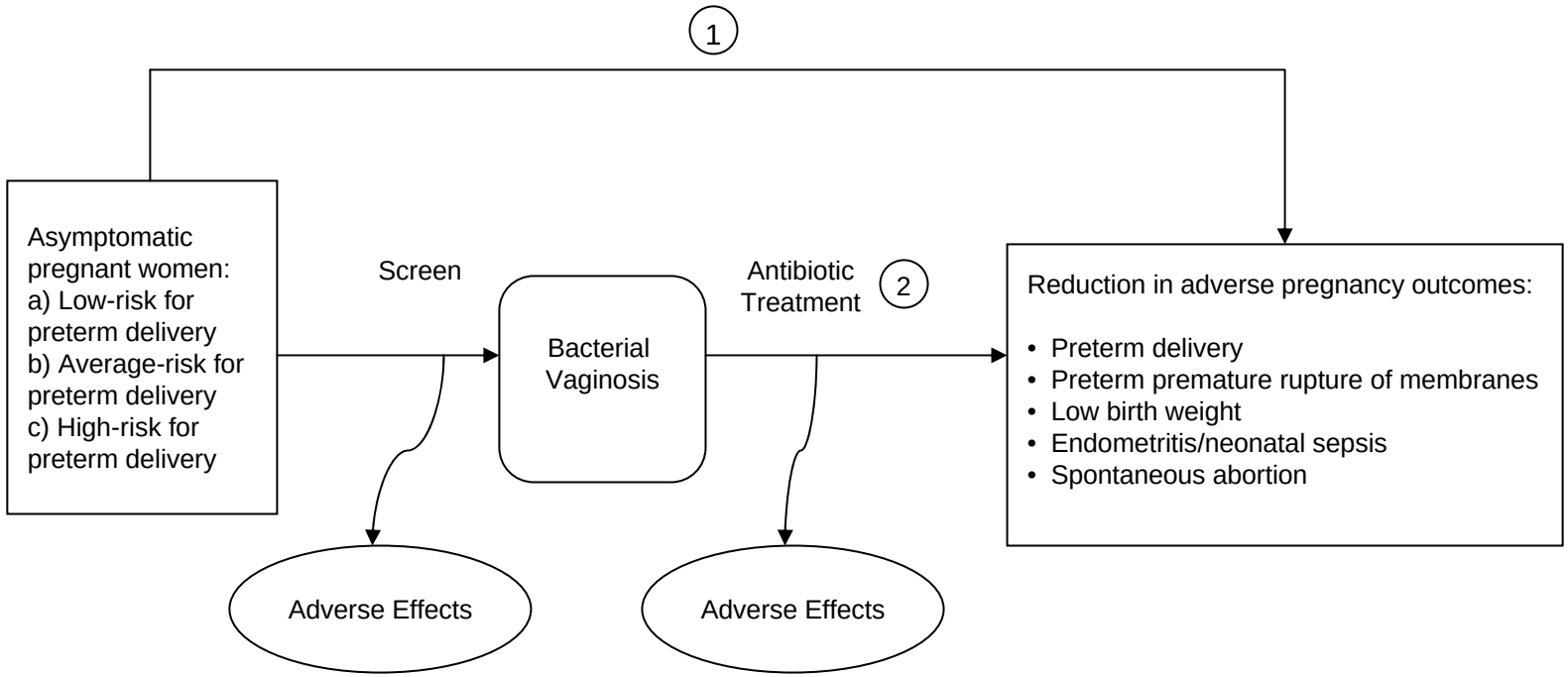
REFERENCES

1. Guise JM, Mahon S, Aickin M, et al. *Screening for Bacterial Vaginosis in Pregnancy. Systematic Evidence Review No. 1 (Contract 290-97-0017 to the Oregon Health Science University Evidence-based Practice Center, Portland, Oregon. AHRQ Publication No. 01-S001.* Rockville, MD: Agency for Health Research and Quality; April 2001.
2. Guise JM, Mahon SM, Aickin M, et al. Screening for bacterial vaginosis in pregnancy. *Am J Prev Med.* 2001;20(3 Suppl):62-72.
3. U. S. Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy: recommendations and rationale. *Am J Prev Med.* 2001;20(3 Suppl):59-61.
4. Yudin MH. Bacterial vaginosis in pregnancy: diagnosis, screening, and management. *Clin Perinatol.* 2005;32(3):617-627.
5. Amsel R, Totten P, Spiegel C, et al. Nonspecific vaginistis. Diagnostic criteria and mircobial and epidemiologic associations. *Am J Med.* 1983;74:14-22.
6. Gravett M, Nelson H, DeRouen T, et al. Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. *JAMA.* 1986;256:1899-1903.
7. Gravett M, Hummel D, Eschenbach D, et al. Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. *Obstet Gynecol.* 1986;67:229-237.
8. Hillier S, Martius J, Krohn MA, et al. A case-control study of choropamnionic infection and histologic chorioamnionitis in prematurity. *N Engl J Med.* 1988;319:972-978.
9. Goldenberg RL, Iams JD, Mercer BM, et al. The preterm prediction study: the value of new vs. standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. *Am J Public Health.* 1998;88(2):233-238.
10. Hillier S, Nugent RP, Eschenbach D, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. *N Engl J Med.* 1995;333:1737-1742.
11. Meis P, Goldene, Mercer B, et al. The preterm prediction study: significance of vaginal infections. National Institute of Child Health and Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol.* 1995;173:1231-1235.
12. Carey JC, Yaffe S, Catz C. The vaginal infections and prematurity study: an overview. *Clin Obstet Gynecol.* 1993;36:809-820.
13. Kurki T, Sivonen A, Renkonen O, et al. Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstet Gynecol.* 1992;80:173-177.
14. Minkoff H, Grunebaum A, Schwarz R, et al. Risk factors for prematurity and premature rupture of membranes: a prospective study of the flora in pregnancy. *Am J Obstet Gynecol.* 1984;150:965-972.
15. Klebanoff MA, Hillier SL, Nugent RP, et al. Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? *Am J Obstet Gynecol.* 2005;192(2):470-477.
16. Azargoon A, Darvishzadeh S. Association of bacterial vaginosis, trichomonas vaginalis, and vaginal acidity with outcome of pregnancy. *SO - Arch Iran Med.* 9(3):213-7, 2006 Jul.
17. Hillier S, Krohn MA, Nugent RP, et al. Characteristics of the three vaginal flora patterns assessed by gram stain among pregnant women. Vaginal infections and prematurity study group. *Am J Obstet Gynecol* 1992;166:938-944.
18. Pastore LM, Royce RA, Jackson TP, et al. Associations between bacterial vaginosis and fetal fibronectin at 24-29 weeks' gestation. *Obstet Gynecol.* 1999;93:117-123.
19. Goldenberg RL, Klebanoff M, Nugent RP, et al. Bacterial colonization of the vagina during pregnancy in four ethnic groups. *Am J Obstet Gynecol.* 1996;174:1618-1621.
20. French JI, McGregor JA, Parker R. Readily treatable reproductive tract infections and preterm birth among black women. *SO - Am J Obstet Gynecol.* 194(6):1717-26; discussion 1726-7, Jun. 2006.
21. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ.* 2004;329(7462).
22. Kekki M, Kurki T, Pelkonen J, et al. Vaginal clindamycin in preventing preterm birth and peripartal infections in asymptomatic women with bacterial vaginosis: a randomized, controlled trial. *Obstet Gynecol.* 2001;97(5 Pt 1):643-648.
23. Hay PE, Morgan D, Ison C, et al. A longitudinal study of bacterial vaginosis during pregnancy. *Br J Obstet Gynaecol.* 1994;101:1048 -1053.
24. Klebanoff MA, Hauth JC, MacPherson CA, et al. Time course of the regression of asymptomatic bacterial vaginosis in pregnancy with and without treatment. *Am J Obstet Gynecol.* 2004;190(2):363-370.
25. Nugent RP, Krohn MA, Hillier S. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol.* 1991;29:297-301.
26. Speigel C, Amsel R, Holmes KK. Diagnosis of bacterial vaginosis by direct gram stain of vaginal fluid. *J Clin Microbiol.* 1983;18:170-177.
27. Honest H, Bachmann LM, Knox EM, et al. Accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review. *BJOG.* 2004;111(5):409-422.
28. Hauth JC, Macpherson C, Carey JC, et al. Early pregnancy threshold vaginal pH and Gram stain scores predictive of subsequent preterm birth in asymptomatic women. *Am J Obstet Gynecol.* 2003;188(3):831-835.

29. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med.* 2000;342(8):534-540.
30. Mastrobattista JM, Bishop KD, Newton ER. Wet smear compared with gram stain diagnosis of bacterial vaginosis in asymptomatic pregnant women. *Obstet Gynecol.* 2000;96(4):504-506.
31. Gratacos E, Figueras F, Barranco M, et al. Prevalence of bacterial vaginosis and correlation of clinical to Gram stain diagnostic criteria in low risk pregnant women. *Eur J Epidemiol.* 1999;15(10):913-916.
32. Centers for Disease Control and Prevention. 1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR.* 1998;47:1-111.
33. Brocklehurst P, Hannah M, McDonald H. The management of bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev.* 1998.
34. McDonald H, Brocklehurst P, Parsons J. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev*. Issue 2. Available at: http://www.cochrane.org/reviews/en/ab000262.html Accessed: May 25, 2006.
35. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. *Obstet Gynecol.* 2005;105(4):857-868.
36. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. *Clin Obstet Gynecol.* 2004;47(4):796-807.
37. Koumans EH, Markowitz LE, Hogan V, et al. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. *Clin Infect Dis.* 2002;35(Suppl 2):S152-172.
38. Leitich H, Brunbauer M, Bodner-Adler B, et al. Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis. *Am J Obstet Gynecol.* 2003;188(3):752-758.
39. Thinkhamrop J, Hofmeyr Gy, Adetoro O, et al. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality [Systematic Review]. *Cochrane Database Syst Rev.* 2005;4:4.
40. Tebes CC, Lynch C, Sinnott J. The effect of treating bacterial vaginosis on preterm labor. *Infect Dis Obstet Gynecol.* 2003;11(2):123-129.
41. Varma R, Gupta JK. Antibiotic treatment of bacterial vaginosis in pregnancy: multiple meta-analyses and dilemmas in interpretation. *Eur J Obstet Gynecol Reprod Biol.* 2006;124:10-14.
42. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002 - Diseases characterized by vaginal discharge. *MMWR.* 2002;51(RR-6):43.
43. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Assessment of risk factors for preterm birth - Clinical management guidelines for obstetrician-gynecologists. No 31. *Obstet Gynecol.* 2001;98(4):709-716.
44. British Association for Sexual Health and HIV and the Clinical Effectiveness Group. Revised national guideline for the management of bacterial vaginosis. Available at: http://www.bashh.org/guidelines/draft/draft_bv_guidelines_2004.doc. Accessed: May 31, 2006.
45. National Institutes of Health. Vaginitis Due to Vaginal Infections. Available at: http://www.niaid.nih.gov/factsheets/vaginitis.htm. Accessed: May 31, 2006.
46. American Academy of Family Physicians. Recommendations for Clinical Preventive Services - Bacterial Vaginosis. Available at: http://www.aafp.org/online/en/home/clinical/exam/a-e.html. Accessed: May 31, 2006.
47. National Institute of Clinical Excellence. Antenatal care: Routine care for the healthy pregnant woman. 2003. Available at: http://www.nice.org.uk/guidance/CG6. Accessed: Nov 11, 2006.
48. CIA World Factbook. Available at: http://www.cia.gov/cia/publications/factbook/. Accessed: June 1, 2006.
49. Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol.* 1995;48(1):9-18.
50. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force. A review of the process. *Am J Prev Med.* 2001;30(3S):21-35.
51. Jadad A, Moore R, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1-12.
52. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;44(11):1271-1278.
53. Furlan AD, Clarke J, Esmail R, et al. A critical review of reviews on the treatment of chronic low back pain. *Spine.* 2001;26(7):E155-162.
54. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med.* 1999;18:2693-2708.
55. Egger M, Davey G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.
56. Terrin N, Schmid C, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol.* 2005;58:894-901.
57. Rembold C. Number needed to screen: development of a statistic for disease screening. *BMJ.* 1998;317:307-312.
58. Odendaal HJ, Popov I, Schoeman J, et al. Labour-is bacterial vaginosis involved? *S Afr Med J.* 2002;92(3):231-234.
59. Kurkinen-Raty M, Vuopala S, Koskela M, et al. A randomised controlled trial of vaginal clindamycin for early pregnancy bacterial vaginosis. *BJOG.* 2000;107(11):1427-1432.

60. Larsson PG, Fahraeus L, Carlsson B, et al. Late miscarriage and preterm birth after treatment with clindamycin: a randomised consent design study according to Zelen. *BJOG.* 2006;113(6):629-637.
61. Lamont R, Duncan S, Mandal D, et al. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol.* 2003;101(3):516-522.
62. Guaschino S, Ricci E, Franchi M, et al. Treatment of asymptomatic bacterial vaginosis to prevent preterm delivery: a randomised trial. *Eur J Obstet Gynecol Reprod Biol.* 2003;110(2):149-152.
63. McGregor JA, French JI, Jones W, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. *Am J Obstet Gynecol.* 1994;170(4):1048-1059
64. Joesoef MR, Hillier SL, Wiknjosastro G, et al. Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight. *Am J Obstet Gynecol.* 1995;173(5):1527-1531.
65. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial. *BJOG.* 1997;104(12):1391-1397.
66. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med.* 1995;333(26):1732-1736.
67. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. *Am J Obstet Gynecol.* 1994;171(2):345-347.
68. Vermeulen G, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous birth in women with increased risk: a randomised placebo-controlled double-blind study. *BJOG.* 1999;106:652-657.
69. Andrews WW, Goldenberg RL. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned from an antibiotic trial in fetal fibronectin positive women. *Semin Perinatol.* 2003;27(3):231-238.
70. Diav-Citrin O, Shechtman S, Gotteiner T, et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. *Teratology.* 2001;63(5):186-192.
71. Sorensen HT, Larsen H, Jensen ES, et al. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. *J Antimicrob Chemother.* 1999;44(6):854-856.
72. Czeizel AE, Rockenbauer M, Czeizel AE, et al. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. *BJOG.* 1998;105(3):322-327.
73. Thapa PB, Whitlock JA, Brockman Worrell KG, et al. Prenatal exposure to metronidazole and risk of childhood cancer: a retrospective cohort study of children younger than 5 years. *Cancer.* 1998;83(7):1461-1468.
74. Ugwumadu A, Manyonda I, Reid F, et al. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet.* 2003;361(9362):983-988.
75. Yudin MH, Landers DV, Meyn L, et al. Clinical and cervical cytokine response to treatment with oral or vaginal metronidazole for bacterial vaginosis during pregnancy: a randomized trial. *Obstet Gynecol.* 2003;102(3):527-534.

Figure 1. Analytic Framework and Key Questions

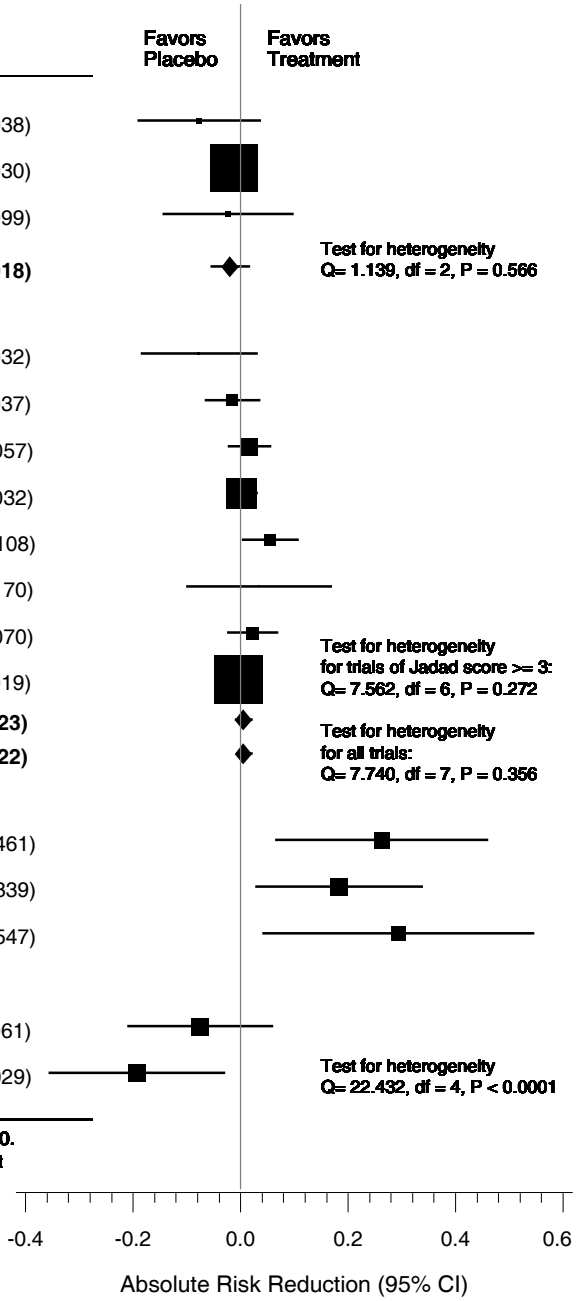


Critical Key Questions:

1. Does screening for bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
    a. low-risk for preterm delivery?
    b. average-risk for preterm delivery?
    c. high-risk for preterm delivery?
2. Does treatment of bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
    a. low-risk for preterm delivery
    b. average-risk for preterm delivery
    c. high-risk for preterm delivery

Figure 2. Study characteristics and absolute risk reduction of preterm delivery (PTD) <37 weeks

	Jadad score	Number of subjects Completed/Randomized	PTD <37 weeks in placebo group	Treatment drug	Number of rounds	Treatment timing	ARR* (95% CI)
Low-Risk Women							
Kurkenin-Raty, 2000	3	101/101	6.0	Vaginal Clindamycin	1	<=20wks	-0.077 (-0.192, 0.038)
Kekki, 2001	4	375/375	3.7	Vaginal Clindamycin	1	<=20wks	-0.011 (-0.052, 0.030)
Odendaal, 2002	3	148/150	15.9	Oral Metronidazole	2	span*	-0.023 (-0.145, 0.099)
All Trials Combined							**-0.019 (-0.056, 0.018)**
Average-Risk Women							
McGregor, 1994	3	129/142	7.2	Vaginal Clindamycin	1	span	-0.077 (-0.186, 0.032)
Joesoef, 1995	4	681/745	13.5	Vaginal Clindamycin	1	span	-0.015 (-0.067, 0.037)
McDonald, 1997	4	480/495	6.3	Oral Metronidazole	2	span	0.0166 (-0.024, 0.057)
Carey, 2000	5	1919/1953	9.4	Oral Metronidazole	2	span	0.0030 (-0.026, 0.032)
Lamont, 2003	5	368/409	9.8	Vaginal Clindamycin	2	<=20wks	0.0551 (0.0027, 0.108)
Guaschino, 2003	2	100/112	15.7	Vaginal Clindamycin	1	span	0.0344 (-0.101, 0.170)
Kiss, 2004	4	292/297	5.7	Vaginal Clindamycin	2	<=20wks	0.0224 (-0.025, 0.070)
Larsson, 2006	4	819/819	2.4	Vaginal Clindamycin	2	<20wks	-0.003 (-0.024, 0.019)
Trials (Jadad score >= 3) Combined							**0.006 (-0.011, 0.023)**
All Trials Combined							**0.006 (-0.009, 0.022)**
High-Risk Women							
Morales, 1994	4	80/94	44.4	Oral Metronidazole	1	<=20wks	0.2630 (0.0646, 0.461)
Hauth, 1995	4	177/177	57.1	Oral Metronidazole	2	>=20wks	0.1830 (0.0269, 0.339)
McDonald, 1997**	4	34/34	35.3	Oral Metronidazole	1	span	0.2940 (0.0408, 0.547)
Vermeulen, 1999	4	16/22	21.2	Vaginal Clindamycin	2	>=20wks	Not Reported
Carey, 2000**	5	210/213	22.5	Oral Metronidazole	2	span	-0.075 (-0.211, 0.061)
Odendaal, 2002**	3	121/127	23.5	Oral Metronidazole	2	span	-0.193 (-0.358,-0.029)



*ARR, absolute risk reduction, difference in probability of PTD <37 weeks (control - treatment); span, treatment timing spans less than 20 and greater than 20.

** McDonald (1997) and Carey (2000) performed a high-risk group sub-analysis; high risk group is included in total study population of the average risk target group; Odendaal (2002) includes 2 target populations; high risk and low risk groups are 2 separate groups.

Figure 3. Absolute risk reduction of preterm delivery (PTD) <34 weeks and PTD <32 weeks

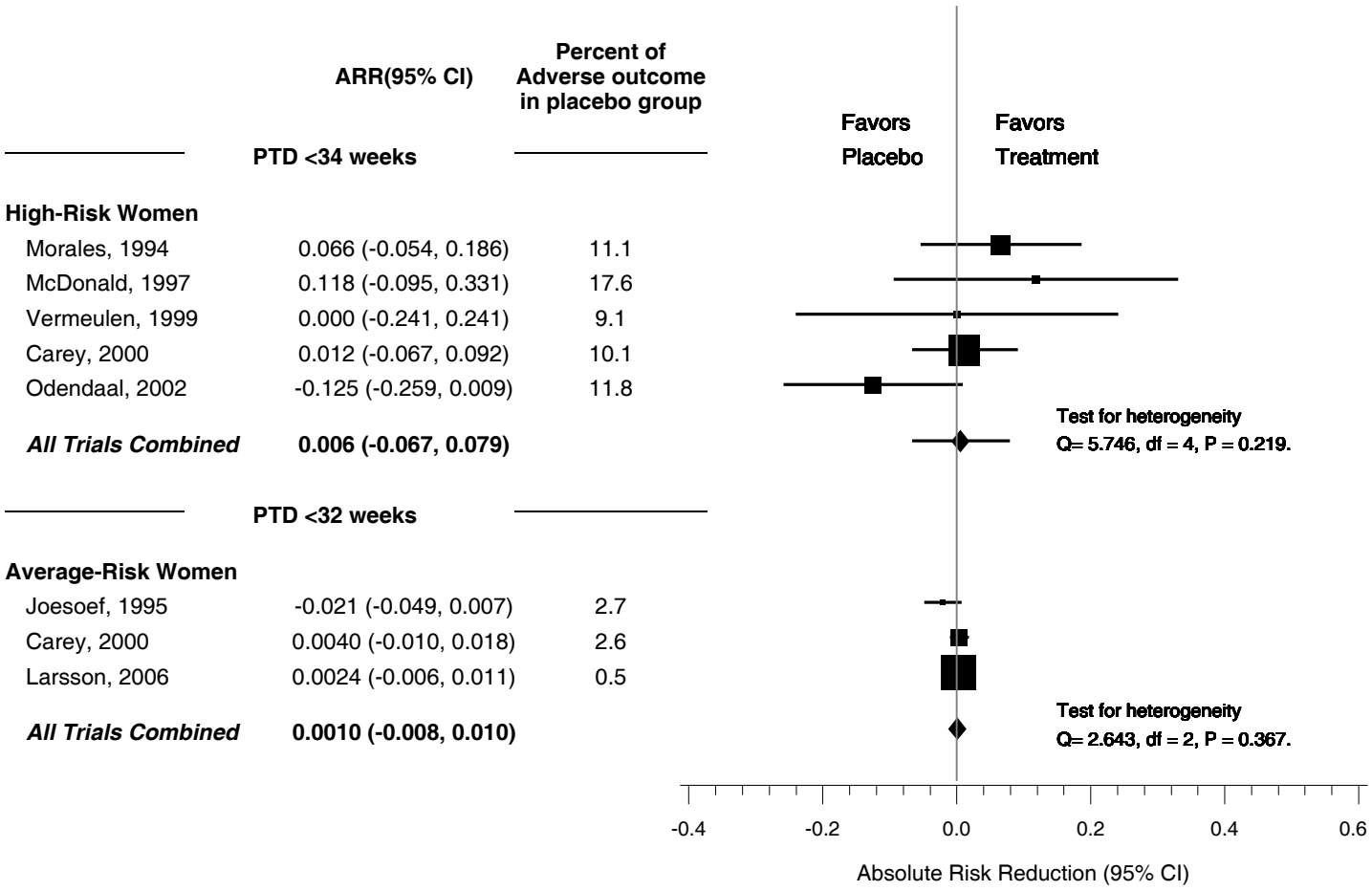
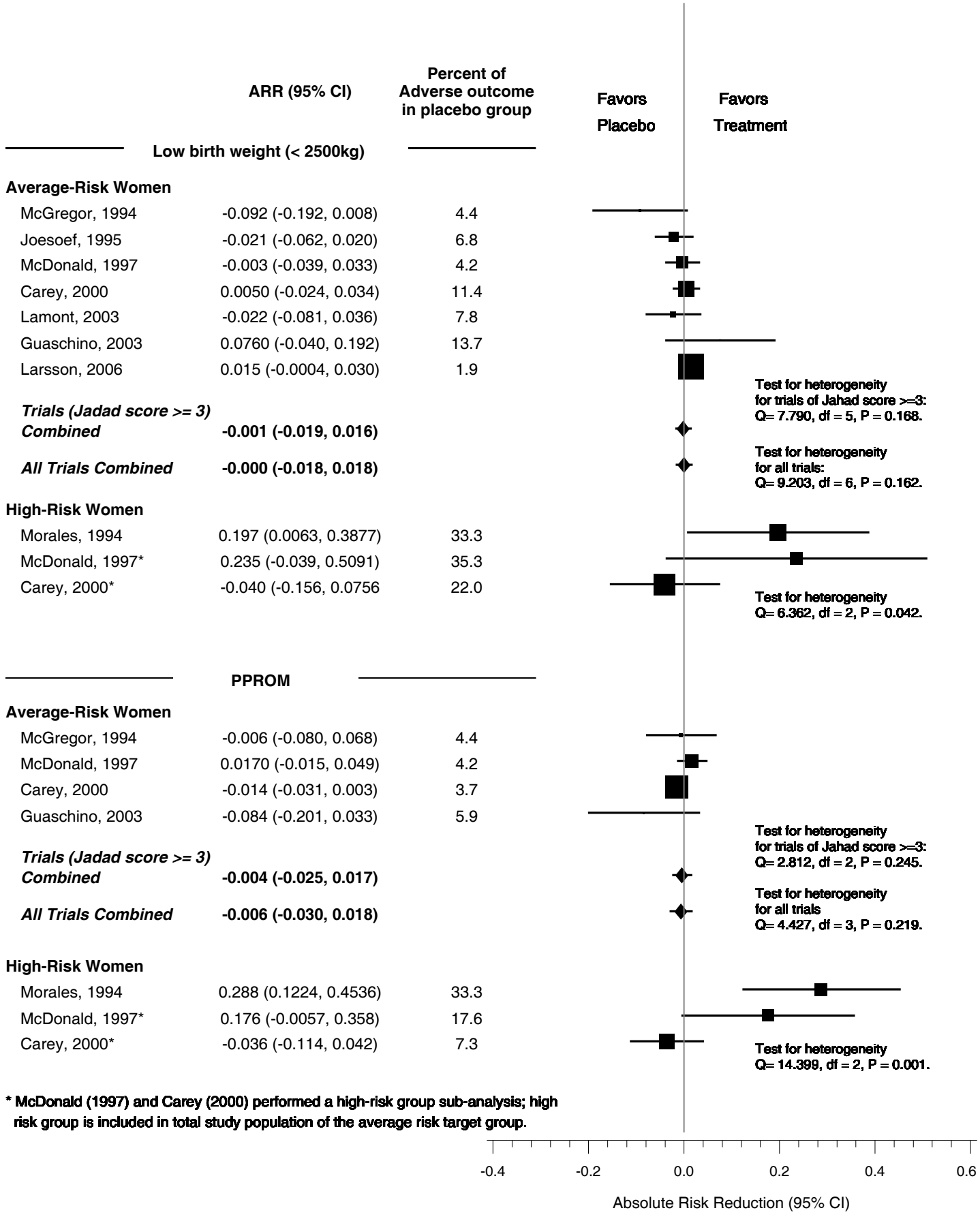


Figure 4. Absolute risk reduction of low birth weight (< 2500g) and preterm premature rupture of membranes (PPROM)



* McDonald (1997) and Carey (2000) performed a high-risk group sub-analysis; high risk group is included in total study population of the average risk target group.

Table 1. Descriptive Characteristics, Percentage of PTD <37 Weeks in BV-positive Women, and Effect Sizes of Included Studies

Study (Jadad score)	N completed/ randomized	Screening method (at weeks gestation)	Treatment route, drug, dosage	PTD<37wks in untreated BV+ women (%)	PTD<37wks in treated BV+ women (%)	Absolute Risk Reduction (ARR) (95% CI)				
						PTD < 37 weeks	PTD < 34 weeks	PTD < 32 weeks	PPROM	LBW <2500g
Low-risk Women										
Kekki, 2001[22] (4)	375/ 375	Gram stain (10 to 17)	Vaginal clindamycin 7d	3.7	4.8	-0.011 (-0.052, 0.030)	--	--	--	--
Kurkinen-Raty, 2000[59] (3)	101/ 101	Gram stain (12)	Vaginal clindamycin 7d	6.0	13.7	-0.077 (-0.192, 0.038)	--	--	--	--
Odendaal, 2002[58] (3)	148/ 150	Gram stain + Amsel (15 to 26)	Oral metronidazole 400mg BID 2d	15.9	18.2	-0.023 (-0.145, 0.099)	0.019 (-0.044, 0.081)	--	--	--
Average-risk Women										
Carey, 2000[29] (5)	1919/ 1953	Gram stain (16 to 24)	Oral Metronidazole 2g repeat @48hr	9.4	9.1	0.003 (-0.026, 0.032)	--	0.004 (-0.010, 0.018)	-0.014 (-0.031, 0.003)	0.005 (-0.024, 0.034)
Guaschino, 2003[62] (2)	100/ 112	Gram stain (14 to 25)	Vaginal Clindamycin 7d	15.7	12.3	0.034 (-0.101, 0.170)	--	--	-0.084 (-0.201, 0.033)	0.076 (-0.040, 0.192)
Joesoef, 1995[64] (4)	681/ 745	Gram stain (14 to 26)	Vaginal clindamycin 7d	13.5	15.0	-0.015 (-0.067, 0.037)	--	-0.021 (-0.049, 0.007)	--	-0.021 (-0.062, 0.020)
Kiss, 2004[21] (4)	292/ 297	Gram stain (15 to 20)	Vaginal Clindamycin 6d	5.7	3.5	0.022 (-0.025, 0.070)	--	--	--	--
Lamont, 2003[61] (4)	368/ 409	Gram stain (13 to 20)	Vaginal clindamycin 3d	9.8	4.3	0.055* (0.003, 0.108)	--	--	--	-0.022 (-0.081, 0.036)
McDonald, 1997[65] (4)	480/ 495	Gram stain (16 to 26)	Oral Metronidazole 400mg BID 2d	6.3	4.6	0.0166 (-0.024, 0.0571)	--	--	0.017 (-0.015, 0.049)	-0.003 (-0.039, 0.033)
McGregor, 1994[63] (3)	129/ 142	Gram stain + Amsel (16 to 27)	Vaginal clindamycin 7d	7.2	14.9	-0.077 (-0.186, 0.032)	--	--	-0.006 (-0.080, 0.068)	-0.092 (-0.192, 0.008)
Larsson, 2006[60] (4)	819/819	Gram stain (>=6)	Vaginal clindamycin 7d	2.4	2.7	-0.003 (-0.024, 0.019)	--	0.0024 (-0.006, 0.011)	--	0.015 (-0.0004, 0.030)

Table 1. Descriptive Characteristics, Percentage of PTD <37 Weeks in BV-positive Women, and Effect Sizes of Included Studies

Study (Jadad score)	N completed/ randomized	Screening method (at weeks gestation)	Treatment route, drug, dosage	PTD<37wks in untreated BV+ women (%)	PTD<37wks in treated BV+ women (%)	Absolute Risk Reduction (ARR) (95% CI)				
						PTD < 37 weeks	PTD < 34 weeks	PTD < 32 weeks	PPROM	LBW <2500g
High-risk Women										
Carey, 2000[29] (5)[†]	210/ 213	Gram stain (16 to 23)	Oral Metronidazole 2g repeat @48hr	22.5	30.0	-0.075 (-0.211, 0.061)	0.012 (-0.067, 0.091)	--	-0.036 (-0.114, 0.042)	-0.040 (-0.156, 0.076)
Hauth, 1995[66] (4)	177/ 177	Amsel (<24)	Oral metronidazole 250mg TID 7d + erythromycin 333mg TID 14d	57.1	38.8	0.183* (0.027, 0.339)	--	--	--	--
McDonald, 1997[65] (4)[†]	34/ 34	Gram stain (16 to 26)	Oral Metronidazole 400mg BID 2d	35.3	5.9	0.294* (0.041, 0.547)	0.118 (-0.095, 0.331)	--	0.176 (-0.006, 0.358)	0.235 (-0.039, 0.509)
Morales, 1994[67] (4)	80/ 94	Amsel (13 to 20)	Oral Metronidazole 250mg TID 7d	44.4	18.1	0.263* (0.065, 0.461)	0.066 (-0.054, 0.186)	--	0.288* (0.122, 0.454)	0.197* (0.006, 0.388)
Odendaal, 2002[58] (3)[‡]	121/ 127	Gram stain + Amsel (15 to 26)	Oral Metronidazole 400mgBID 2d	23.5	42.9	-0.193* (-0.358, -0.029)	-0.125 (-0.259, 0.009)	--	--	--
Vermeulen, 1999[68] (4)	16/ 22	Gram stain (<26)	Vaginal Clindamycin 7d	--	--	--	0.000 (-0.241, 0.241)	--	--	--

*Significant at $p < 0.05$

[†]Carey 2000 and McDonald 1997 performed a subgroup analyses of high-risk women. These women are included in the total population of average-risk women in these respective studies.

[‡]Odendaal 2002 included two distinct populations: low risk women (i.e. primigravidae) and high risk women (i.e. history of PTD or other risk factor).

-- means not reported

Negative (-) sign indicates increase in adverse events (treatment harm)

Positive (+) sign indicates a decrease in adverse event (i.e. treatment benefit)

Table 2. Absolute Risk Reduction (ARR)* Pooled Results for BV Treatment - Randomized Trials by Risk Level**

	Absolute Risk Reduction (ARR) (95% Confidence Interval)				
	PTD < 37 weeks	**PTD < 34 weeks**	**PTD < 32 weeks**	**PPROM**	**LBW <2500g**
Low-risk	-0.019 (-0.056, 0.018)	--	--	--	--
Average-risk	0.006 (-0.009, 0.022)	--	0.0010 (-0.008, 0.010)	-0.006 (-0.030, 0.018)	-0.000 (-0.018, 0.018)
High-risk	Not pooled	0.006 (-0.067, 0.079)	--	Not pooled	Not pooled

*ARR: difference in probability (control - treatment)

Negative (-) sign indicates increase in adverse events (treatment harm)
Positive (+) sign indicates a decrease in adverse event (treatment benefit)

**See Table 1 for specific data by study and risk level. Low-risk study references: 22, 58, 59; average-risk study references: 21, 29, 60, 61, 62, 63, 64, 65; high-risk study references: 29, 58, 65, 66, 67, 68.

Abbreviations: LBW, Low birth weight; PPROM, Preterm premature rupture of membranes; PTD, Preterm delivery.

Table 3. Study Characteristics of Women at High Risk for PTD <37 Weeks

Study (Jadad score)	Target population or Subset	HR criteria / definition of analyzed subset	Setting	Race*	Mean age (y)*	Other	N completed/ randomized	Screening method (at weeks gestation)	Treatment drug, route	2nd round of treatment	PTD<37 wks in untreated BV+ women (%)	PTD<37 wks in treated BV+ women (%)
Carey, 2000[29] (5)[†]	Subset	Hx PTD	Multi-center trial of several university centers, U.S.	White 14.8% Black 69.5% Hispanic 15.7%	23.0	--	210/ 213	Gram stain (16 to 23)	Oral metronidazole 2g repeat @48hr	Yes	22.5	30.0
Hauth, 1995[66] (4)	Target	Hx PTD (analyzed subset) or pre-pregnancy wt <50 kg	University of Alabama, US	Black 73.6%	23.7	--	177/ 177	Amsel (>20)	Oral metronidazole 250mg TID 7d + Oral erythromycin 333mg TID 14d	Yes	57.0	38.8
McDonald, 1997[65] (4)[†]	Subset	Hx PTD	4 perinatal centers in a large metro area in Australia	White 87.4% Black NR Asian 8.6% Aboriginal 1%	26.2	--	34/ 34	Gram stain (16 to 26)	Oral metronidazole 400mg BID 2d	Yes	35.3	5.9
Morales, 1994[67] (4)	Target	Penult.PTD from PTL or PPROM	University, Baltimore, US	Black 47.5%	24.8	Hx >1 PTD in 50% Tx, 39% C	80/ 94	Amsel (<=20)	Oral metronidazole 250mg TID 7d	No	39.0	18.1
Odendaal, 2002[58] (3)[‡]	Target	Hx PTD or midtrimester abortion	South Africa, NOS	NR	27.5	--	121/ 127	Gram stain + Amsel (15 to 26)	Oral metronidazole 400mg BID 2d	Yes	24.0	42.9
Vermeulen, 1999[68] (4)	Target	Penult.PTD s/PPROM	12 city hospitals in the Netherlands	NR	31.1	Hx>1 PTD[§] in 8% Tx, 8% C	16/ 22	Gram stain (>20)	Vaginal clindamycin 7d	Yes	--	--

*The data for race, age, and marital status reflect the total population in each study, which may include women without BV or history of PTD.

[†]Carey 2000 and McDonald 1997 performed subgroup analyses of high-risk BV-positive women. These women are included in the total population of average-risk women in these respective studies.

[‡]Odendaal 2002 included two distinct populations: low-risk women (i.e. primigravidae) and high risk women (i.e. history of PTD or other risk factor).

[§]Includes BV-positive and BV-negative women.

Abbreviations: Penult.=penultimate pregnancy; PTD = spontaneous preterm delivery; Hx PTD = history of spontaneous preterm delivery in any prior pregnancy; PTL = idiopathic preterm labor; Tx=Treatment; C=Control

-- data not reported

Table 4. Summary of Evidence Regarding the Benefits of Screening 1000 High-risk* Pregnant Women for Bacterial Vaginosis

Benefit and Relevant Factors	General high risk group PTD baseline risk <30%	"More selected" high risk group PTD baseline risk > 30%
Assumptions		
Proportion of pregnant women who meet criteria for screening	0.10	0.03
Prevalence of BV in population	0.25	0.25
Relative risk of PTD in patients with BV	1.60	1.60
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 BV (Prob in control group - Prob in treated group, and 95% CI) †		
PTD<37 weeks	-0.125 (-0.239 to -0.010)[29, 58]	+0.229 (+0.118 to +0.339)[65-67]
PPROM	-0.036 (-0.114 to +0.042)[29]	+0.237 (+0.115 to +0.360)[65, 67]
PTD<34 weeks	-0.033 (-0.126 to +0.060) [29, 58]	+0.079 (-0.026 to +0.183)[65, 67]
Effect sizes in patients without BV (Prob in control group - Prob in treated group)		
PTD<37 weeks	0.00	0.00
PPROM	0.00	0.00
PTD<34 weeks	-0.02	-0.06
Results		
# of patients with unsuspected BV	250	250
# correctly diagnosed to have BV	238	238
# of patients with BV who complete therapy	190	190
# with BV missed	13	13
# correctly diagnosed to not have BV	713	713
# incorrectly diagnosed to have BV	38	38
# of patients without BV who complete therapy	30	30
# WITH BV missed or don't complete therapy	60	60
# WITHOUT BV who don't complete therapy	720	720
Outcomes		
Decrease or increase in PTD<37 weeks	-24 (-45 to -2)	+44 (+22 to +64)
Decrease or increase in PPROM	-7 (-22 to +8)	+45 (+22 to +68)
Decrease or increase in PTD<34 weeks	-7 (-25 to +11)	+13 (-7 to +33)

Negative sign (-) indicates a net increase in adverse outcomes (harm)
Positive sign (+) indicates a net decrease in adverse outcomes (benefit)

*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".

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

Table 5. Summary of the Evidence

Critical Key Question	Assessment of Quality: Linkage Level*	Reviewed Evidence/Comment
KQ 1. Does **screening** for bacterial vaginosis during pregnancy reduce adverse pregnancy outcomes? In women at low, average, or high-risk for preterm delivery?	Poor	No studies found.
KQ 2. Does **treatment** of bacterial vaginosis during pregnancy reduce adverse pregnancy outcomes?		
A. In women at **low-risk** for preterm delivery	Good	3 RCTs[22, 58, 59]; meta-analysis PTD <37 weeks, ARR -0.019, 95% CI -0.056 to 0.018: no treatment effect.†
B. In women at **average-risk** for preterm Delivery	Good‡	8 RCTs[21, 29, 60- 65] [4 from 2001 report]; meta-analysis PTD <37 weeks, ARR 0.006, 95% CI -0.009 to 0.022: no treatment effect.
C. In women at **high-risk** for preterm delivery	Fair	5 RCTs[29, 58, 65-67] [4 from 2001 report]; no treatment effect; significant heterogeneity. 3 show significant treatment benefit, one shows significant treatment harm, and one shows no effect of treatment.
KQ 3. What **adverse effects** does **screening** for bacterial vaginosis have on pregnancy outcomes?	Fair	No studies directly address this question; potential harm (increased risk for PTD) for misdiagnosis (BV negative patients receiving treatment) [2 from previous report, Hauth[66] & Carey[29]]; Andrews[69] showed potential harm of misdiagnosis, but it did not reach statistical significance.
KQ 3. What **adverse effects** does the **treatment** of bacterial vaginosis have on pregnancy outcomes?	Fair	Observational studies; congenital abnormalities; no association with metronidazole (confirms 2001 report findings). Retrospective cohort; cancer outcomes, mixed results. RCT's; tolerability, no differences between oral and vaginal clindamycin treatment and control groups. Systematic Review; oral and vaginal metronidazole showed high compliance and tolerability.

*In evaluating the quality of the body of evidence concerning the linkages in the analytic framework, the topic team considers 3 criteria for a good, fair, or poor rating:

1. Aggregate internal validity
2. Aggregate external validity
3. Coherence / consistency

Reference: Harris, R., Helfand, M., Woolf, SH, Lohr, KN, Mulrow, CD, Teutsch, SM, Atkins, D. (2001). Current methods of the U.S. Preventive Services Task Force: A review of the process. American Journal of Preventive Medicine, 20 (Suppl 3): 21-35.

†Negative sign (-) indicates treatment harm; Positive sign (+) indicates treatment benefit.

‡One RCT categorized data as average-risk; however, it is more likely a low-risk population. See average-risk category.

Appendix A. Search Strategies

Specific Searches Per Key Question:

Key Question 1 - Screening
Database: Ovid MEDLINE

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

Key Question 2 - Treatment
Database: Ovid MEDLINE

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

Key Question 3 – Adverse Effects
Database: Ovid MEDLINE

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)

Continued…

Appendix A. Search Strategies

Overall Searches:

Database: 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

Database: 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

Database: 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

Database: Pre-Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

1 vaginosis.mp.
2 (prematur$ 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 B. Inclusion and Exclusion Criteria

Inclusion Criteria:

Evaluates screening and/or treatment adverse effects and pregnancy outcomes for women with bacterial vaginosis (BV) and:

Study designs: systematic reviews, randomized control trials, or comparative effectiveness studies
Populations: pregnant women at low, average or high risk for preterm delivery
Publication years: studies included in previous review, and new studies published from 1996 - 2006
Health outcomes: preterm delivery, premature rupture of membranes, low birth weight, spontaneous abortion, endometritis/neonatal sepsis
Conducted in a U.S. applicable country
Primary care feasible or referable: see end of appendix for definitions

Exclusion Criteria:

Does not evaluate screening and/or treatment adverse effects and pregnancy outcomes for women with BV

Study designs: Editorials, letters, non-systematic reviews, non-comparative studies, case control studies, case studies, protocol (no data), comment/opinion, etc.
Populations: non-pregnant women, symptomatic for BV, multiple gestation
Selective population not normally seen in primary care (e.g. patients recruited from ER or other specialty setting who are injured or on drugs and do not represent a general patient population)
Study not conducted in a country applicable to the U.S. population
Non-humans
Non-English language
Health Outcomes: Does not report designated outcomes
Setting: Intervention not done in primary care, primary care-feasible, or widely available for primary care referral
Study quality: Does not meet criteria for quality

Overall Criteria for Judging if an Intervention is Primary Care *Feasible*:

Whom Targeted: Somehow involve individual-level identification of being a patient/in need of intervention
Who Delivered: Usually involve primary care clinicians (physicians in family practice, internal medicine, ob-gyn, pediatricians, GP), other physicians, nurses, nurse practitioners, or physician's assistants, or related clinical staff (dietitians, health educators, others counselors) in some direct or indirect way—or, at least, the intervention would be seen as connected to the health care system by the participant.
How Delivered: To individuals or in small groups (15 or less). Do not involve only or primarily group-level interventions outside the primary care setting to achieve behavioral changes. Generally involve no more than 8 group sessions total and intervention time period is no longer than 12 months.
Where Delivered: Could be delivered anywhere (including via the web, interactive technologies, in the home) if linked to primary care as above.

Definition of Primary Care *Referable*:

In order for an intervention to be feasible for primary care *referral*, it would need to be conducted as part of a healthcare setting or else be widely available in the community at a national level (such as a car seat fitting station within a hospital).

Appendix C. Excluded Studies at the Full Text Level

1. Alanen A. Does screening reduce preterm births? *BMJ*. 2004;329(7462):374. **Wrong study design**
2. Ancel PY. Perspectives in the prevention of premature birth. *Eur J Obstet Gynecol Reprod Biol*. 2004;117 Suppl 1:S2-5. **Wrong study design**
3. Andrews WW, Hauth JC, Goldenberg RL. Infection and preterm birth. *Am J Perinatol.* 2000;17(7):357-365. **Wrong study design**
4. Andrews WW, Sibai BM, Thom EA, et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. *Obstet Gynecol.* 2003;101(5 Pt 1):847-855. **Evaluates risk factors**
5. Andy C. Antibiotic use and preterm labor: attitudes and practice patterns of North Carolina obstetric providers. *J Women's Health.* 2003;12(9):903-909. **Wrong study design**
6. Arredondo JL, Higuera F, Hidalgo H, et al. Clindamycin vaginal cream vs. oral metronidazole in the treatment of bacterial vaginosis. *Arch STD HIV Res.* 1992;6(3):183-195. **Wrong study design**
7. Arredondo JL, Higuera F, Lourdes NM, et al. New treatment alternatives in bacterial vaginosis. *Ginecol Obstet Mex*. 1994;62(AUG):226-234. **Wrong study design**
8. Audisio T, Penacino M, Cannistraci R, et al. Detection of bacterial vaginosis, Trichomonas vaginalis infection, and vaginal Candida infection: a comparative study of methods of extracting exudates, with and without a speculum, during pregnancy. *J Low Genit Tract Dis.* 2005;9(4):213-215. **Evaluates test efficacy**
9. Azargoon A, Darvishzadeh S. Association of bacterial vaginosis, trichomonas vaginalis, and vaginal acidity with outcome of pregnancy. *Arch Iran Med.* 9(3):213-7, 2006. **Evaluates risk factors**
10. Balu RB, Savitz DA, Ananth CV, et al. Bacterial vaginosis and vaginal fluid defensins during pregnancy. *Am J Obstet Gynecol.* 2002;187(5):1267-1271. **Out of scope of review**
11. Bayo M, Berlanga M, Agut M. Vaginal microbiota in healthy pregnant women and prenatal screening of group B streptococci (GBS). *Int Microbiol.* 2002;5(2):87-90. **Prevalence data only**
12. Begum A, Nilufar S, Akther K, et al. Prevalence of selected reproductive tract infections among pregnant women attending an urban maternal and childcare unit in Dhaka, Bangladesh. *J Health Popul Nutr.* 2003;21(2):112-116. **Prevalence data only**
13. Benedetto C, Tibaldi C, Marozio L, et al. Cervicovaginal infections during pregnancy: epidemiological and microbiological aspects. *J Matern Fetal Neonatal Med.* 2004;16 Suppl 2:9-12. **Wrong study design**
14. Berger A, Kane KY. Clindamycin for vaginosis reduces prematurity and late miscarriage. *J Fam Pract.* 2003;52(8):603-604. **Wrong study design**
15. Boskey ER, Atherly-Trim SA, O'Campo PJ, et al. Acceptability of a self-sampling technique to collect vaginal smears for gram stain diagnosis of bacterial vaginosis. *Women's Health Issues.* 2004;14(1):14-18. **Evaluates test efficacy**
16. Brocklehurst P, Hannah M, McDonald H. Interventions for treating bacterial vaginosis in pregnancy.[update in Cochrane Database Syst Rev. 2003;(2):CD000262; PMID: 12804393]. *Cochrane Database Syst Rev*. 2000 (2): CD000262. **Wrong study design**
17. Brown D, Jr. Clinical variability of bacterial vaginosis and trichomoniasis. *J Reprod Med.* 2004;49(10):781-786. **Wrong study design**
18. Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol.* 1995;172:525-529. **Covered by previous report**
19. Camargo RP, Simoes JA, Cecatti JG, et al. Impact of treatment for bacterial vaginosis on prematurity among Brazilian pregnant women: a retrospective cohort study. *Sao Paulo Medical Journal/Revista Paulista de Medicina* 123(3):108-12, 2005 May 2. **Wrong study design**
20. Carey JC, Klebanoff MA. Is a change in the vaginal flora associated with an increased risk of preterm birth? *Am J Obstet Gynecol.* 2005;192(4):1341-1346. **Wrong study design**
21. Carey JC, Klebanoff MA. Bacterial vaginosis and other asymptomatic vaginal infections in pregnancy. *Curr Womens Health Rep.* 2001;1(1):14-19. **Wrong study design**
22. Carey JC, Klebanoff MA. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What have we learned about vaginal infections and preterm birth? *Semin Perinatol.* 2003;27(3):212-216. **Covered by previous report**
23. Caro-Paton T, Carvajal A, Martin de Diego I, et al. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol.* 1997;44(2):179-182. **Wrong study design**
24. Chaijareenont K, Sirimai K, Boriboonhirunsarn D, et al. Accuracy of Nugent's score and each Amsel's criteria in the diagnosis of bacterial vaginosis. *J Med Assoc Thai.*2004;87(11):1270-1274. **Evaluates test efficacy**
25. Chandran R. Cochrane for clinicians: putting evidence into practice. Screening for and treating asymptomatic bacterial vaginosis in pregnancy. *Am Fam Physician.* 2002;66(5):780-782. **Wrong study design**
26. Dodd JM, Flenady V, Cincotta R, et al. Prenatal administration of progesterone for preventing preterm birth. *Cochrane Database of Systematic Reviews.* 2005. **Out of scope of review**
27. Cottrell BH, Shannahan M. Maternal bacterial vaginosis and fetal/infant mortality in eight

Appendix C. Excluded Studies at the Full Text Level

Florida counties, 1999 to 2000. *Public Health Nurs.* 2004;21(5):395-403. **Wrong study design**

28. Culhane JF, Desanto D, Goldenberg RL, et al. Variation in Nugent score and leukocyte count in fluid collected from different vaginal sites. *Obstet Gynecol.* 2005;105(1):120-123. **Evaluates test efficacy**
29. Darwish AM, Makarem MH, Alnashar EM, et al. Screening for bacterial vaginosis in high-risk pregnancy: the experience of a developing country. *Acta Obstet Gynecol Scand.* 2005;84(5):483-485. **Wrong study design**
30. Donders GG. Treatment of sexually transmitted bacterial diseases in pregnant women. *Drugs*. 2000;59(3):477-485. **Wrong study design**
31. Duff P, Lee ML, Hillier SL, et al. Amoxicillin treatment of bacterial vaginosis during pregnancy. *Obstet Gynecol.* 1991;77(3):431-435. **Out of scope of review**
32. Eckert LO, Moore DE, Patton DL, et al. Relationship of vaginal bacteria and inflammation with conception and early pregnancy loss following in-vitro fertilization. *Infect Dis Obstet Gynecol*. 2003;11(1):11-17. **Wrong population**
33. Fiorilli A, Molteni B, Milani M. Successful treatment of bacterial vaginosis with a policarbophil-carbopol acidic vaginal gel: results from a randomised double-blind, placebo-controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 2005;120(2):202-205. **Wrong population**
34. French JI, McGregor JA, Parker R. Readily treatable reproductive tract infections and preterm birth among black women. *Am J Obstet Gynecol.*194(6):1717-26;2006. **Wrong study design**
35. Gjerdingen D, Fontaine P, Bixby M, et al. The impact of regular vaginal pH screening on the diagnosis of bacterial vaginosis in pregnancy. *J Fam Pract.* 2000;49(1):39-43. **Evaluates test efficacy**
36. Goffinet F. Primary predictors of preterm labour. *BJOG.* 2005;112 Suppl 1:38-47. **Evaluates risk factors**
37. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000;342(20):1500-1507. **Wrong study design**
38. Greene JF, 3rd, Kuehl TJ, Allen SR. The papanicolaou smear: inadequate screening test for bacterial vaginosis during pregnancy. *Am J Obstet Gynecol.* 2000;182(5):1048-1049. **Evaluates test efficacy**
39. Hauth JC, Macpherson C, Carey JC, et al. Early pregnancy threshold vaginal pH and Gram stain scores predictive of subsequent preterm birth in asymptomatic women. *Am J Obstet Gynecol*. 2003;188(3):831-835. **Wrong study design**
40. Hitti J, Hillier SL, Agnew KJ, et al. Vaginal indicators of amniotic fluid infection in preterm labor. *Obstet Gynecol.* 2001;97(2):211-219. **Wrong population**
41. Hollier LM, Workowski K. Treatment of sexually transmitted diseases in women. *Obstet Gynecol Clin North Am.* 2003;30(4):751-775. **Wrong study design**
42. Honest H, Bachmann LM, Knox EM, et al. The accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review. *BJOG*. 2004;111(5):409-422. **Evaluates test efficacy**
43. Hoyme UB, Saling E. Efficient prematurity prevention is possible by pH-self measurement and immediate therapy of threatening ascending infection. *Eur J Obstet Gynecol Reprod Biol.* 2004;115(2):148-153. **Evaluates test efficacy**
44. Jacobsson B, Pernevi P, Chidekel L, et al. Bacterial vaginosis in early pregnancy may predispose for preterm birth and postpartum endometritis. *Acta Obstet Gynecol Scand.* 2002;81(11): 1006-1010. **Wrong study design**
45. Jeffcoat MK, Geurs NC, Reddy MS, et al. Periodontal infection and preterm birth. *J Am Dent Assoc.* 2001;132:875-878. **Out of scope of review**
46. Jeffcoat MK, Geurs NC, Reddy MS, et al. Current evidence regarding periodontal disease as a risk factor for preterm birth. *Ann Periodontol.* 2001;6:183-188. **Out of scope of review**
47. Joesoef M, Schmid G. Bacterial vaginosis. *Clin Evid.* 2003(10):1824-1833. **Wrong study design**
48. Kalinka J, Hanke W, Wasiela M, et al. Socioeconomic and environmental risk factors of bacterial vaginosis in early pregnancy. *J Perinat Med.* 2002;30(6): 467-475. **Evaluates risk factors**
49. Kalinka J, Laudanski T, Hanke W, et al. Do microbiological factors account for poor pregnancy outcome among unmarried pregnant women in Poland? *Fetal Diagn Ther*. 2003;18(5):345-352. **Evaluates risk factors**
50. Kazy Z, Puho E, Czeizel AE. The possible association between the combination of vaginal metronidazole and miconazole treatment and poly-syndactyly Population-based case-control teratologic study. *Reprod Toxicol.* 2005;20(1):89-94. **Wrong study design**
51. Kazy Z, Puho E, Czeizel AE. Gestational age and prevalence of preterm birth after vaginal metronidazole treatment during pregnancy. *Int J Gynaecol Obstet.* 2004;87(2):161-162. **Wrong study design**
52. Kekki M, Kurki T, Kotomaki T, et al. Cost-effectiveness of screening and treatment for bacterial vaginosis in early pregnancy among women at low risk for preterm birth. Acta Obstet Gynecol Scand. 2004;83(1):27-36. **Wrong study design**
53. Kekki M, Kurki T, Kurkinen-Raty M, et al. Recurrent bacterial vaginosis in pregnancy predisposes to infectious morbidity: a double-blind, placebo-controlled multicenter intervention trial with vaginal clindamycin. *Int J Gynecol*

Appendix C. Excluded Studies at the Full Text Level

Obstet. 1999;67(Suppl 2). **Covered by prior report**

54. Kekki M, Kurki T, Paavonen J, et al. Insulin-like growth factor binding protein-1 in cervix as a marker of infectious complications in pregnant women with bacterial vaginosis. *Lancet.* 1999;353(9163). **Out of scope of review**
55. Kekki M, Kurki T, Polkonen J, et al. Bacterial vaginosis in pregnancy is associated with infectious morbidity - a randomized placebo-controlled trial with vaginal clindamycin. *Acta Obstet Gynecol Scand.* Vol. 1996;75(87). **Covered by prior report**
56. Kekki M, Kurki TP, Polkonen J, et al. Bacterial vaginosis in pregnancy is associated with increased infectious morbidity - a randomized placebo-controlled intervention trial with vaginal clindamycin. *Cochrane Database Syst Rev.* 1996; vol 75. **Covered by prior report**
57. King EA, Britt R, McFarlane JM, Hawkins C. Bacterial vaginosis and Chlamydia trachomatis among pregnant abused and nonabused Hispanic women. *JOGN Nurs.* 2000;29(6):606-612. **Prevalence data only**
58. Kirkham C, Harris S, Grzybowski S. Evidence-based prenatal care: part II. Third-trimester care and prevention of infectious diseases. *Am Fam Physician.* 2005;71(8):1555-1560. **Wrong study design**
59. Klebanoff MA, Hauth JC, MacPherson CA, et al. Time course of the regression of asymptomatic bacterial vaginosis in pregnancy with and without treatment. *Am J Obstet Gynecol.* 2004;190(2):363-370. **Wrong study design**
60. Klebanoff MA, Hillier SL, Nugent RP, et al. Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? *Am J Obstet Gynecol.* 2005;192(2):470-477. **Wrong study design**
61. Klein LL, Gibbs RS. Use of microbial cultures and antibiotics in the prevention of infection-associated preterm birth. *Am J Obstet Gynecol.* 2004;190(6):1493-1502. **Wrong study design**
62. Koumans EH, Kendrick JS. Preventing adverse sequelae of bacterial vaginosis: a public health program and research agenda. *Sex Transm Dis.* 2001;28(5): 292-297. **Wrong study design**
63. Koumans EH, Markowitz LE, Hogan V, et al. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. *Clin Infect Dis.* 2002;35(Suppl 2):S152-172. **Wrong study design**
64. Lamont RF. Infection in the prediction and antibiotics in the prevention of spontaneous preterm labour and preterm birth. *BJOG.* 2003;110 Suppl 20:71-75. **Wrong study design**
65. Lamont RF, Jones BM, Mandal D, et al. The efficacy of vaginal clindamycin for the treatment of abnormal genital tract flora in pregnancy. *Infect Dis Obstet Gynecol.* 2003;11(4):181-189. **Evaluates test efficacy**
66. Lamont RF. Recent evidence associated with the condition of preterm prelabour rupture of the membranes. *Curr Opin Obstet Gynecol.* 2003;15(2):91-99. **Out of scope of review**
67. Lamont RF, Sheehan M, Morgan DJ, et al. Safety and efficacy of clindamycin intravaginal cream for the treatment of bacterial vaginosis in pregnancy: a randomized, double-blind, placebo-controlled multicenter study. *Int J Gynecol Obstet.* 1999;67(Suppl 2). **Covered by prior report**
68. Lamont RF, Taylor-Robinson D. Review of the accuracy of various diagnostic tests for bacterial vaginosis to predict preterm birth. *BJOG.* 2005;112(2):259-260. **Evaluates test efficacy**
69. Larsson PG, Bergstrom M, Forsum U, et al. Bacterial vaginosis. Transmission, role in genital tract infection and pregnancy outcome: an enigma. *APMIS.* 2005;113(4):233-245. **Wrong study design**
70. Larsson PG, Forsum U. Bacterial vaginosis--a disturbed bacterial flora and treatment enigma. *APMIS.* 2005;113(5):305-316. **Out of scope of review**
71. Lazar PA. Does oral metronidazole prevent preterm delivery in normal-risk pregnant women with asymptomatic bacterial vaginosis? *J Fam Pract.* 2000;49(6):495-496. **Covered by prior report**
72. Leitich H, Bodner-Adler B, Brunbauer M, et al. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. *Am J Obstet Gynecol.* 2003;189(1):139-147. **Wrong study design**
73. Leitich H, Brunbauer M, Bodner-Adler B, et al. Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis. *Am J Obstet Gynecol.* 2003;188(3):752-758. **Wrong study design**
74. Libman MD, Kramer M, Platt R, et al. Comparison of Gram and Kopeloff stains in the diagnosis of bacterial vaginosis in pregnancy. *Diagn Microbiol Infect Dis.* 2006 Mar;54(3):197-201. **Evaluates test efficacy**
75. Mastrobattista JM, Bishop KD, Newton ER. Wet smear compared with gram stain diagnosis of bacterial vaginosis in asymptomatic pregnant women. *Obstet Gynecol.* 2000;96(4):504-506. **Evaluates test efficacy**
76. Mathew R, Kalyani J, Bibi R, et al. Prevalence of bacterial vaginosis in antenatal women. *Indian J Pathol Microbiol.* 2001;44(2):113-116. **Wrong study design**
77. McDonald H, Brocklehurst P, Parsons J. Antibiotics for treating bacterial vaginosis in pregnancy [Systematic Review]. *Cochrane Database Syst Rev.* 2005;4:4. **Wrong study design**
78. McDonald H, Brocklehurst P, Parsons J. Antibiotics for treating bacterial vaginosis in pregnancy [Systematic Review]. *Cochrane Database Syst Rev.* 2006:2. **Wrong study design**

Appendix C. Excluded Studies at the Full Text Level

79. McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Bacterial vaginosis in pregnancy and efficacy of short-course oral metronidazole treatment: a randomized controlled trial. *Obstet Gynecol.* 1994;84(3): 343-348. **Covered by prior report**
80. McGregor JA, French JI, Parker R, et al. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation. *Am J Obstet Gynecol.* 1995;173(1): 157-167. **Out of scope of review**
81. McGregor JA, French JI, Seo K. Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 1991;165(4 Pt 1):867-875. **Covered by prior report**
82. Mertz HL, Ernest JM. Antibiotics and preterm labor. *Current Women's Health Reports*. 2001;1(1):20-26. **Wrong study design**
83. Miller L, Thomas K, Hughes JP, et al. Randomised treatment trial of bacterial vaginosis to prevent post-abortion complication. *BJOG.* 2004;111(9):982-988. **Out of scope of review**
84. Molteni B, D'Antuono A, Bandini P, et al. Efficacy and tolerability of a new chlorhexidine-based vaginal gel in vaginal infections. *Curr Med Res Opin.* 2004;20(6):849-853. **Wrong population**
85. Morgan DJ, Aboud CJ, McCaffrey IM, et al. Comparison of Gram-stained smears prepared from blind vaginal swabs with those obtained at speculum examination for the assessment of vaginal flora. *BJOG*. 1996;103(11):1105-1108. **Covered by prior report**
86. Myers ER. Screening for bacterial vaginosis to prevent preterm birth: assessing effectiveness and cost-effectiveness. *Acta Obstet Gynecol Scand.* 2004;83(1):2-3. **Wrong study design**
87. National Institute of Clinical Excellence. Antenatal care: Routine care for the healthy pregnant woman. 2003. Available at: http://www.nice.org.uk/guidance/CG6. Accessed Nov 11, 2006. **Wrong study design**
88. Nelson DB, Bellamy S, Gray TS, Nachamkin I. Self-collected versus provider-collected vaginal swabs for the diagnosis of bacterial vaginosis: an assessment of validity and reliability. *J Clin Epidemiol.* 2003;56(9):862-866. **Evaluates test efficacy**
89. Nelson DB, Macones G. Bacterial vaginosis in pregnancy: current findings and future directions. *Epidemiol Rev.* 2002;24(2):102-108. **Wrong study design**
90. Neri A, Sabah G, Samra Z. Bacterial vaginosis in pregnancy treated with yoghurt. *Acta Obstet Gynecol Scand.* 1993;72(1):17-19. **Out of scope of review**
91. Oakeshott P, Hay P, Hay S, et al. Association between bacterial vaginosis or chlamydial infection and miscarriage before 16 weeks' gestation: prospective community based cohort study. *BMJ*. 2002;325(7376):1334. **Wrong study design**
92. Obata-Yasuoka M, Ba-Thein W, Hamada H, et al. A multiplex polymerase chain reaction-based diagnostic method for bacterial vaginosis. *Obstet Gynecol.* 2002;100(4):759-764. **Evaluates test efficacy**
93. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. *Obstet Gynecol.* 2005;105(4):857-868. **Wrong study design**
94. Ovalle A, Martinez MA, Kakarieka E, et al. Antibiotic administration in patients with preterm premature rupture of membranes reduces the rate of histological chorioamnionitis: a prospective, randomized, controlled study. *J Matern Fetal Neonatal Med.* 2002;12(1):35-41. **Out of scope of review**
95. Pastore LM, King TS, Dawson IJ, et al. Prospective validation of a perinatal bacterial vaginosis screening risk score. *J Perinatol.* 2004;24(12): 735-742. **Evaluates test efficacy**
96. Pastore LM, Thorp JM, Jr., Royce RA, et al. Risk score for antenatal bacterial vaginosis: BV PIN points. *J Perinatol.* 2002;22(2):125-132. **Evaluates test efficacy**
97. Pawlaczyk M, Friebe Z, Pawlaczyk MT, et al. The effect of treatment for vaginal yeast infection on the prevalence of bacterial vaginosis in early pregnancy. *Acta Dermatovenerol Croat.* 2006;14(1):26-29. **Out of scope of review**
98. Potter B, Jhorden L, Alfonsi G. Clinical inquiries. Should we screen for bacterial vaginosis in asymptomatic patients at risk for preterm labor? J Fam Pract. 2004;53(10):827-831. **Wrong study design**
99. Purwar M, Ughade S, Bhagat B, et al. Bacterial vaginosis in early pregnancy and adverse pregnancy outcome. *J Obstet Gynaecol Res.* 2001;27(4):175-181. **Wrong study design**
100. Ramsey PS, Lyon MD, Goepfert AR, et al. Use of vaginal polymorphonuclear to epithelial cell ratios for the prediction of preterm birth. *Obstet Gynecol.* 2005;105(1):139-144. **Wrong study design**
101. Raynes-Greenow CH, Roberts CL, Bell JC, et al. Antibiotics for ureaplasma in the vagina in pregnancy [Systematic Review]. *Cochrane Database Syst Rev*. 2005;4:4. **Evaluates test efficacy**
102. Reid G, Burton J, Devillard E. The rationale for probiotics in female urogenital healthcare. *MedGenMed.* 2004;6(1):49. **Wrong population**
103. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. *Clin Obstet Gynecol.* 2004;47(4): 796-807. **Wrong study design**
104. Romero R, Espinoza J, Chaiworapongsa T, et al. Infection and prematurity and the role of preventive strategies. Semin Neonatal. 2002;7:259-274. **Wrong study design**

Appendix C. Excluded Studies at the Full Text Level

105. Rosenstein IJ, Morgan DJ, Lamont RF, et al. Effect of intravaginal clindamycin cream on pregnancy outcome and on abnormal vaginal microbial flora of pregnant women. *Infect Dis Obstet Gynecol.* 2000;8(3-4):158-165. **Wrong study design**
106. Rosenstein IJ, Morgan DJ, Sheehan M, et al. Effect of topical clindamycin on bacterial vaginosis and outcome of pregnancy. *Int J Gynecol Obstet.* 1999;67(Suppl 2). **Covered by prior report**
107. Rosnes J, Network NM. Does vaginal ph or gram stain score alter the likelihood of successful metronidazole treatment of bacterial vaginosis or trichomonas vaginalis during pregnancy. *Am J Obstet Gynecol.* 2002;187(6 (Pt 2). **Evaluates test efficacy**
108. Schmidt H, Hansen JG. Validity of wet-mount bacterial morphotype identification of vaginal fluid by phase-contrast microscopy for diagnosis of bacterial vaginosis in family practice. *APMIS.* 2001;109(9):589-594. **Evaluates test efficacy**
109. Schoeman J, Steyn PS, Odendaal HJ, et al. Bacterial vaginosis diagnosed at the first antenatal visit better predicts preterm labour than diagnosis later in pregnancy. *J Obstet Gynecol.* 2005;25(8):751-753. **Wrong study design**
110. Sheffield JS, Andrews WW, Klebanoff MA, et al. Spontaneous resolution of asymptomatic Chlamydia trachomatis in pregnancy. *Obstet Gynecol.* 2005;105(3):557-562. **Out of scope of review**
111. Shennan A, Crawshaw S, Briley A, et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. *BJOG.*2006 Jan;113(1):65-74. **Wrong population**
112. Shimano S, Nishikawa A, Sonoda T, et al. Analysis of the prevalence of bacterial vaginosis and Chlamydia trachomatis infection in 6083 pregnant women at a hospital in Otaru, Japan. *J Obstet Gynaecol Res.* 2004;30(3):230-236. **Prevalence data only**
113. Smaill F. Antibiotics for asymptomatic bacteriuria in pregnancy [Systematic Review]. *Cochrane DatabaseSyst Rev.* 2005;4:4. **Out of scope of review**
114. Smart S, Singal A, Mindel A. Social and sexual risk factors for bacterial vaginosis. *Sex Transm Infect.* 2004;80(1):58-62. **Wrong study design**
115. Sobel JD. What's new in bacterial vaginosis and trichomoniasis? *Infect Dis Clin North Am.* 2005;19(2):387-406. **Wrong study design**
116. Stetzer BP, Mercer BM. Antibiotics and preterm labor. *Clin Obstetrics Gynecol.* 2000;43(4):809-817. **Wrong study design**
117. Steyn PS, Odendaal HJ, Schoeman J, et al. A randomised, double-blind placebo-controlled trial of ascorbic acid supplementation for the prevention of preterm labour. *J Obstet Gynaecol.* 2003;23(2):150-155. **Wrong study design**
118. Strauss RA, Eucker B, Savitz DA, et al. Diagnosis of bacterial vaginosis from self-obtained vaginal swabs. *Infect Dis Obstet Gynecol.* 2005;13(1):31-35. **Evaluates test efficacy**
119. Surbek DV, Hoesli IM, Holzgreve W. Morphology assessed by transvaginal ultrasonography differs in patients in preterm labor with vs. without bacterial vaginosis. *Ultrasound Obstet Gynecol.* 2000;15(3):242-245. **Wrong study design**
120. Taylor-Robinson D, Morgan DJ, Sheehan M, et al. Relation between gram-stain and clinical criteria for diagnosing bacterial vaginosis with special reference to gram grade II evaluation. *Int J STD AIDS.* 2003;14(1):6-10. **Evaluates test efficacy**
121. Tebes CC, Lynch C, Sinnott J. The effect of treating bacterial vaginosis on preterm labor. *Infect Dis Obstet Gynecol.* 2003;11(2):123-129. **Wrong study design**
122. Thinkhamrop J, Hofmeyr GJ, Adetoro O, et al. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality [Systematic Review]. *Cochrane Database Syst Rev.* 2005;4:4. **Wrong study design**
123. Tokyol C, Aktepe OC, Cevrioglu AS, et al. Bacterial vaginosis: comparison of Pap smear and microbiological test results. *Mod Pathol.* 2004;17(7): 857-860. **Evaluates test efficacy**
124. Ugwumadu A, Reid F, Hay P, et al. Natural history of bacterial vaginosis and intermediate flora in pregnancy and effect of oral clindamycin. *Obstetrics Gynecol.* 2004;104(1):114-119. **Prevalence data only**
125. Ugwumadu AH. Cervical morphology in pregnancy, bacterial vaginosis and the risk of preterm delivery. *Ultrasound Obstetrics Gynecol.* 2000;15(3):174-176. **Wrong study design**
126. Ugwumadu AH. Bacterial vaginosis in pregnancy. *Curr Opin Obstet Gynecol.* 2002;14(2):115-118. **Wrong study design**
127. Varma R, Gupta JK. Antibiotic treatment of bacterial vaginosis in pregnancy: multiple meta-analyses and dilemmas in interpretation. *Eur J Obstet Gynecol Reprod Biol.* 2006;124:10-14. **Wrong study design**
128. Verhelst R, Verstraelen H, Claeys G, et al. Comparison between Gram stain and culture for the characterization of vaginal microflora: definition of a distinct grade that resembles grade I microflora and revised categorization of grade I microflora. *BMC Microbiol.* 2005;5:61. **Evaluates test efficacy**
129. Vermeulen GM, van Zwet AA, Bruinse HW. Changes in the vaginal flora after two percent clindamycin vaginal cream in women at high risk of spontaneous preterm birth. *BJOG.* 2001;108(7):697-700. **Wrong study design**
130. Vigneswaran R, O'Loughlin JA, McDonald HM, et al. Metronidazole treatment of bacterial

vaginosis in pregnancy, and effect on preterm birth. *Prenat Neonatal Med.* Vol. 1996;1(1). **Wrong study design**

131. Wasiela M, Krzeminski Z, Hanke W, et al. [Diagnostic value of Gram stain for assessment of vaginal smears during pregnancy]. *Med Dosw Mikrobiol.* 2004;56(1):93-98. **Not available in English**
132. Witt A, Petricevic L, Kaufmann U, et al. DNA hybridization test: rapid diagnostic tool for excluding bacterial vaginosis in pregnant women with symptoms suggestive of infection. *J Clin Microbiol.* 2002;40(8):3057-3059. **Evaluates test efficacy**
133. Yen S, Shafer MA, Moncada J, et al. Bacterial vaginosis in sexually experienced and non-sexually experienced young women entering the military. *Obstet Gynaecol.* 2003;102(5 Pt 1):927-933. **Wrong study design**
134. Yudin MH. Bacterial vaginosis in pregnancy: diagnosis, screening, and management. *Clin Perinatol.* 2005;32(3):617-627. **Wrong study design**
135. Yudin MH, Landers DV, Hillier SL. Cytokine profiles in response to bacterial vaginosis in pregnancy before and after treatment with oral or vaginal metronidazole. *Infect Dis Obstet Gynecol.* 2002;10(Suppl 1). **Wrong population**

US Preventive Services Task Force Quality Rating Criteria*

Randomized Controlled Trials (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, cross-overs, adherence, 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 intension-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); 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 maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all 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 subjects) and a "medium" spectrum of patients.

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; 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 cases/controls 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 variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; 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 percent or attention to some but not all important confounding variables.

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

*Created using information from Harris et al. Current Methods of the USPSTF: A Review of the Process. Am J Prev Med. 2001:20(3S);21-35.

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Jadad Scale Criteria†

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

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

A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. [Either give a score of 1 point for each "yes" or 0 points for each "no." There are no in-between marks.]

The final two 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.

Jadad Score Calculation	
Item	**Score**
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1
Deduct one 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

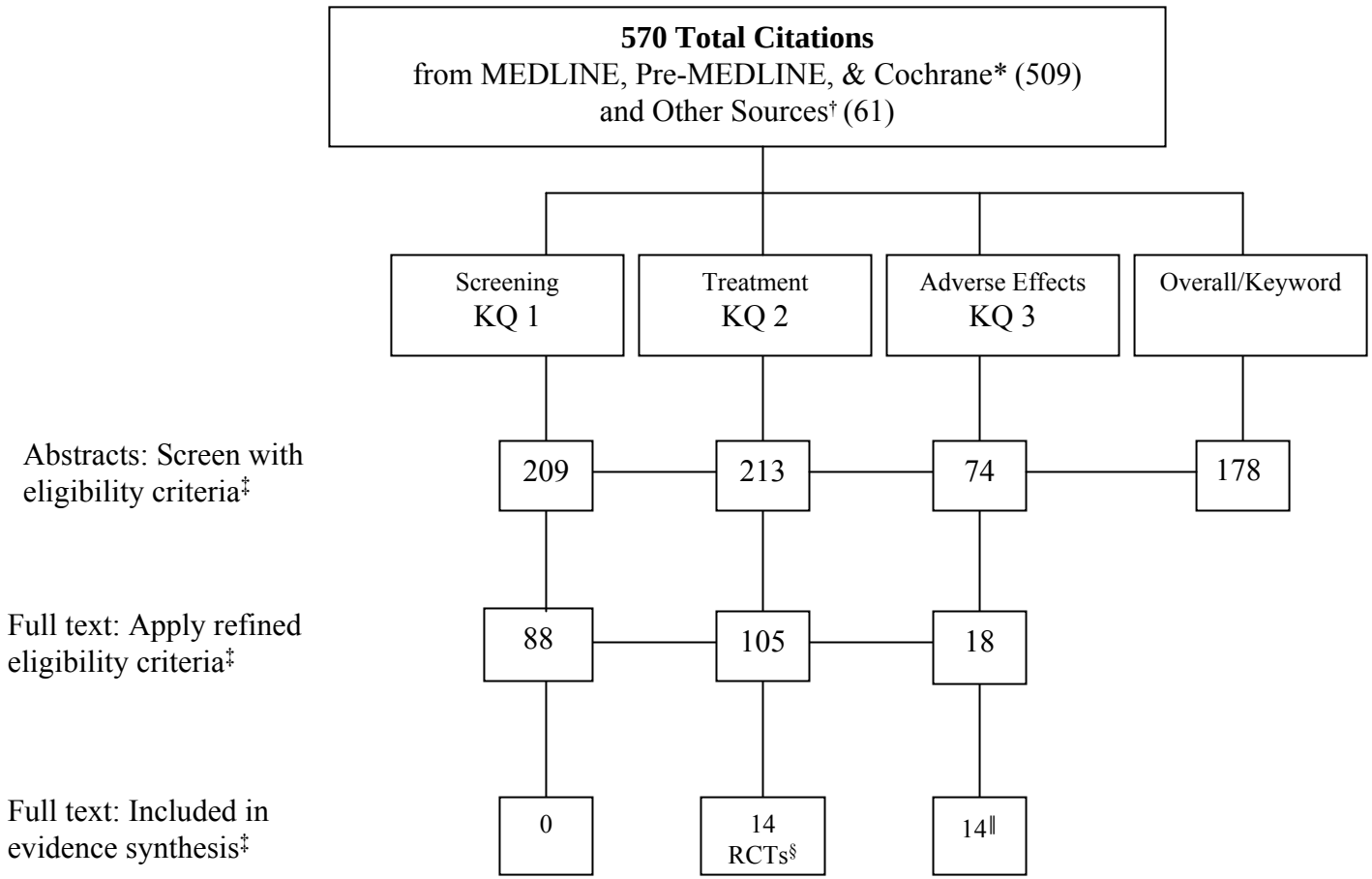
Randomization. A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date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

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 no points.

†Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;17[1]:1-12

Appendix E. Search and Selection of the Literature Tree



*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, expert referrals, etc.

‡ Duplicates exist between key questions at all three search and selection levels

§ 7 trials from the previous 2001 report

‖ 5 studies from the previous 2001 report

Note: 151 abstracts were additionally reviewed non-systematically for the subsidiary question.

Appendix F. Expert Reviewers

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Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Risk Level (Low, Average, High)	Setting/ Country	Inclusion/Exclusion Criteria	Demographics	Number Completed/ Number Enrolled	Treatment and Regimen	Treatment Rounds, *n*
Kekki, 2001[22]	Low	Multi-prenatal clinics, Finland	Exclude multiple pregnancies or women with previous PTD	Mean age, 28.8 y; predominantly white	375 Tx: 187 Placebo: 188	Route: vaginal Dosage: 2% clindamycin cream Duration: 7 days	1
Kurkinen-Raty, 2000[59]	Low	Multi-center, Finland	Exclude multiple pregnancies or women with previous PTD	Mean age, 27.9 y; race, NR; previous PTD, 10%; manual labor, 33%; middle- or upper-level employee, 67%	101/123 Tx: 62 Placebo: 61	Route: vaginal Dosage: 2% clindamycin cream Duration: 7 days	1
Odendaal, 2002[58]	Low, High	South Africa, Tertiary Academic Hospital	Exclude multiple pregnancies and known cervical incompetence, include if antibiotic-free for ≥14 days	Mean age, 21.6 y; race, NR; average unmarried, 86.4%	Both L and H risk: 931/995 Low risk: primigravidae 459/464 BV + Tx: 66/67 BV + Placebo: 82/83 BV - : 311/314 High risk: multigravidae 472/491 BV + Tx: 70/74 BV + Placebo: 51/53 BV - : 351/364	Route: oral Dosage: Metronidazole 400 mg Duration: twice daily for 2 days Placebo (vitamin C 100 mg twice daily for 2 days)	2
Guaschino, 2003[62]	Average	Outpatient OB clinics, multi-center, Italy	Exclude multiple pregnancies; include asymptomatic, antibiotic-free for ≥15 d	Mean age, 29.1 y; race, NR; education, 12.5 y (Tx), 10.8 y (control)	100/112 Tx: 49/55 Control: 51/57	Route: intra-vaginal Dosage: 2% clindamycin cream Duration: 7 days	1

Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Diagnosis - Screening Method (Gram Stain, Amsel)	Timing of Screening/ Treatment (Gestational Age in Weeks)	Spontaneous Preterm Delivery (PTD) < 37 weeks	PTD < 34 weeks	PTD < 32 weeks	PTD < 28 weeks	Low Birth Weight (LBW) (<2500g) or Very Low Birth Weight (<1500 g)	Preterm Premature Rupture of Membranes (PPROM)
Kekki, 2001[22]	Gram stain (Spiegel)	1. 10-17 weeks gestation 2. 1 week post first screening (Tx) 3. 30-36 weeks gestation	Tx: 9/187 Placebo: 7/188	Not reported	Not reported	Not reported	Not reported	Not reported
Kurkinen-Raty, 2000[59]	Gram strain (Spiegel)	1. 12 weeks gestation 2. one week after treatment 3. 30th week gestation	Tx: 7/51 Placebo: 3/50	Not reported	Not reported	Not reported	Not reported	Not reported
Odendaal, 2002[58]	Exam and/or Gram stain (Spiegel)	1. 15-26 weeks gestation 2. 4 weeks post first screening (Tx)	Low risk: primigravidae BV + Tx: 12/66 BV + Placebo: 13/82 BV - : 64/311 High risk: multigravidae BV + Tx: 30/70 BV + Placebo: 12/51 BV - : 102/351	Low risk: primigravidae BV + Tx: 2/66 BV + Placebo: 4/82 BV - : 21/311 High risk: multigravidae BV + Tx: 17/70 BV + Placebo: 6/51 BV - : 42/351	Not reported	Low risk: primigravidae BV + Tx: 1/66 BV + Placebo: 2/82 BV - : 2/311 High risk: multigravidae BV + Tx: 7/70 BV + Placebo: 1/51 BV - : 14/351	Mean weight in grams (standard deviation) Low risk: primigravidae BV + Tx: 2475 (980) BV + Placebo: 2759 (683) BV - : 2752 (792)	Not reported
Guaschino, 2003[62]	Gram Stain / Hillier 1992 (Nugent)	14-25 weeks gestation	Tx: 6 Control: 9	Not reported	Not reported	Not reported	Tx: 3 Control: 7	Tx: 7 Control: 3

Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Inter-Uterine Death (IUD)	Neonatal Death (NND)	Perinatal Death (PND)	Other Outcomes	Adverse Effects	USPSTF Quality Rating (Good, Fair, Poor) & Jadad Score (0-5)
Kekki, 2001[22]	Not reported	Not reported	Not reported	Peripartum infections Tx: 21/187 Placebo: 33/188	Vulvovaginal itching Tx: 6/187 Placebo: 6/188	Fair/Good 4
Kurkinen-Raty, 2000[59]	Not reported	Not reported	Not reported	Puerperal infectious morbidity seen more in cases of persistent BV	Not reported	Fair 3
Odendaal, 2002[58]	Low risk primigravidae BV + Tx: 0/66 BV + Placebo: 2/82 BV - : 5/311 High risk multigravidae BV + Tx: 4/70 BV + Placebo: 1/51 BV - : 12/351	Low risk primigravidae BV + Tx: 1/66 BV + Placebo: 0/82 BV - : 2/311 High risk multigravidae BV + Tx: 3/70 BV + Placebo: 0/51 BV - : 6/351	Low risk primigravidae BV + Tx: 1/66 BV + Placebo: 2/82 BV - : 7/311 High risk multigravidae BV + Tx: 7/70 BV + Placebo: 1/51 BV - : 18/351	Apgar score	Occurrence or absence of adverse effects not reported	Fair 3
Guaschino, 2003[62]	Not reported	Not reported	Not reported	No difference in mean gestational age. Respiratory distress syndrome: 2 Tx (4.1%), 3 controls (5.9%), p=ns.	1 case of suspected fracture of clavicle, randomization assignment not specified.	Poor 2

Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Risk Level (Low, Average, High)	Setting/ Country	Inclusion/Exclusion Criteria	Demographics	Number Completed/ Number Enrolled	Treatment and Regimen	Treatment Rounds, *n*
Kiss, 2004[21]	Average	Non-hospital OB clinics in Vienna, Austria	Exclude multiple pregnancies; include asymptomatic, no vaginal bleeding	Mean age, 28.9 y; race, 98% white	4155/4429	Route: Vaginal Dosage: 2% clindymacin cream Duration: 6 days 2nd round: oral clindamycin	2
Lamont, 2003[61]	Average	Hospital-based ante natal care; 3 sites in UK	Include ages 16-40 y, Gram stain consistent with BV, asymptomatic, 13-20 wk of gestation. Exclusions: history of antibiotic-related colitis, inflammatory bowel disease, or frequent periodic diarrhea; multiple pregnancies; and pregnancy complications.	Mean age, 27 y; race, 70% white, 15% black; previous PTD, 7.3%	368/409 Tx: 178/208 Placebo: 190/201	Route: vaginal Dosage: 2% Clindamycin cream, 5 grams Duration: 3 days	2
Larrson, 2006[60]	Average	Southeast Health Care Region of Sweden	Include ≥18 y, asymptomatic, no antibiotic use in early pregnancy, Swedish-speaking. Exclude multiple pregnancies and other pregnancy complications.	Mean age, 28.5 y; race, 98% white; previous PTD, 9.2% (Tx), 6% (control)	9025 enrolled and screened, 819 found BV+ and randomized: Tx: 408/408 Control: 411/411	Route: intra-vaginal Dosage: clindamycin cream for 7 days, vs. no treatment Duration: 7 days	2 or 3

Abbreviations: A, Average; H, High; L, Low; Tx, Treatment.

Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Diagnosis - Screening Method (Gram Stain, Amsel)	Timing of Screening/ Treatment (Gestational Age in Weeks)	Spontaneous Preterm Delivery (PTD) < 37 weeks	PTD < 34 weeks	PTD < 32 weeks	PTD < 28 weeks	Low Birth Weight (LBW) (<2500g) or Very Low Birth Weight (<1500 g)	Preterm Premature Rupture of Membranes (PPROM)
Kiss, 2004[21]	Gram stain (Nugent score 3+)	15-20 weeks gestation	Tx: 5 Control: 8	Not reported for BV subgroup	Not reported for BV subgroup	Not reported for BV subgroup	Not reported for BV subgroup	Not reported for BV subgroup
Lamont, 2003[61]	Gram stain (Nugent)	1. 13-20 weeks gestation 2. 20-24 days after baseline visit 3. 24-48 hours post delivery	Tx: 8/208 Placebo: 19/201	Not reported	Not reported	Not reported	Tx: 15/193 Control: 18/204	Not reported
Larrson, 2006[60]	Gram stain (Nugent score >=6)	10-14 weeks gestation	Tx: 11 Control: 10	Tx: 2 Control: 4	Tx: 1 Control: 2	NR	Tx: 2 Control: 8	NR

Appendix G - Evidence Table. Descriptive Data on RCT Treatment Trials: 2000-2006

Study & Year	Inter-Uterine Death (IUD)	Neonatal Death (NND)	Perinatal Death (PND)	Other Outcomes	Adverse Effects	USPSTF Quality Rating (Good, Fair, Poor) & Jadad Score (0-5)
Kiss, 2004[21]	Not reported for BV subgroup	Not reported for BV subgroup	Not reported for BV subgroup	Not reported for BV subgroup	None of the women reported adverse effects during the treatment period	Good 4
Lamont, 2003[61]	Tx: 3/140 Control: 1/142	No difference	Not reported	Gestational age at delivery was statistically significantly lower in the placebo group, however it did not have an effect on the pregnancy outcomes.	Occurrence or absence of adverse effects not reported	Good 5
Larrson, 2006[60]	NR	NR	NR	Cumulative days of NICU: Tx: 70 Control: 223	3 women withdrew from treatment because of persistent itching	Good 4