Screening for Bacterial Vaginosis in Pregnancy

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Context: Bacterial vaginosis (BV) is a strong independent risk factor for adverse pregnancy outcomes. BV is found in 9% to 23% of pregnant women. Symptoms include vaginal discharge, pruritus, or malodor, but often women with BV are asymptomatic.

Objectives: To determine whether screening and treating pregnant women for BV reduces adverse pregnancy outcomes, as part of an assessment for the U.S. Preventive Services Task Force.

Data Sources: Randomized clinical trials of BV treatment in pregnancy that measured pregnancy outcomes were identified from multiple searches in MEDLINE from 1966 to 1999, the Cochrane Controlled Trials Register and Library, and national experts.

Study Selection: All randomized controlled trials of BV treatment in pregnancy that specifically measured pregnancy outcomes.

Data Extraction: The following information was abstracted: study design and blinding, diagnostic methods, antibiotic interventions, timing of antibiotic treatment in pregnancy, criteria for treatment, comorbidities, demographic details, risk factors for preterm delivery such as previous preterm delivery, compliance, rates of spontaneous and total preterm delivery less than 37 weeks and less than 34 weeks, preterm premature rupture of membranes, low birth weight less than 2500 grams, spontaneous abortion, postpartum endometritis, and neonatal sepsis. For each study, we measured the effect of treatment by calculating the difference in the rate of a given pregnancy outcome in the control group minus the treatment group (the absolute risk reduction [ARR]). A stepwise procedure based on the profile likelihood was applied to assess heterogeneity, to pool studies when appropriate, and to calculate the mean and 90% confidence intervals (CIs) for the effect of treatment.

Data Synthesis: Seven randomized controlled trials met inclusion criteria for the meta-analysis. We found no benefit to BV treatment in average-risk women for any pregnancy outcome. Results of studies of high-risk populations, women with previous preterm delivery, were statistically heterogeneous. They clustered into two groups; one showed no benefit (ARR=−0.08, 90% CI=−0.19 to 0.04), whereas the three homogeneous studies showed potential benefit of BV treatment (pooled ARR=0.22; 90% CI=0.13 to 0.31) for preterm delivery before 37 weeks. Four high-risk studies reported results for preterm delivery less than 34 weeks. The pooled estimate showed no benefit (ARR=0.04; 90% CI=−0.02 to 0.09), but variation was noted among individual studies. Two trials of high-risk women found an increase in preterm delivery less than 34 weeks in women who did not have BV but received BV treatment. Comparisons of patient populations, treatment regimens, and study designs did not explain the heterogeneity among studies.

Conclusions: We found no benefit to routine BV screening and treatment. A subgroup of high-risk women may benefit from BV screening and treatment; however, there may be a subgroup for whom BV treatment could increase the occurrence of preterm delivery.

Medical Subject Headings (MeSH): bacterial vaginosis, vaginitis, pregnancy, preventive health services, evidence-based medicine, MEDLINE, methods, mass screening (Am J Prev Med 2001;20(3S):62–72)

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The U.S. Preventive Services Task Force recommendations based on this evidence review can be found in Screening for Bacterial Vaginosis in Pregnancy: Recommendations and Rationale, available elsewhere in this supplement, and from the AHRQ Web site and clearinghouse.

0749-3797/01/$–see front matter
PII S0749-3797(01)00256-2

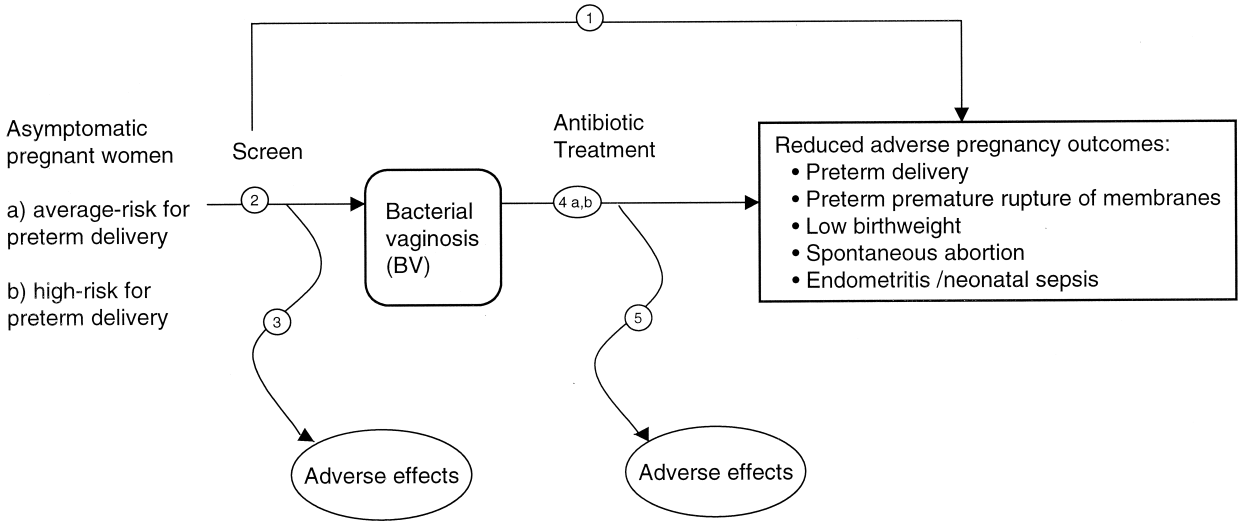

Figure 1. Screening for bacterial vaginosis: analytic framework

Introduction

Bacterial vaginosis 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.[1–3] Once diagnosed, the microflora imbalance can be altered with a short course of antibiotic therapy.

In the 1980s, well-done case–control studies demonstrated an association between BV and adverse pregnancy outcomes.[4] Since then, two large, prospective, longitudinal, multicenter cohort studies[5–8] and several smaller studies[3,9,10] have confirmed these associations. 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 studies of predominantly low-socioeconomic-status women seen at academic medical centers or public hospitals. In several large (N=2899 to 10,397), multicenter, prospective, longitudinal studies performed in these settings, the prevalence of BV ranged from 9% to 23%.[5–7,11,12] In a study of 13,747 pregnant women at seven U.S. academic medical centers from 1984 to 1989 (the Vaginal Infections and Prematurity [VIP] Study), 23% of 5285 African-American women and 9% of 4049 Caucasian women had BV.[13]

The prevalence of BV in pregnant women in community settings is not well studied, and there are no population-based studies of prevalence in the United States. A Finnish study[9] found a prevalence of 21.4% among 790 unselected, healthy, nulliparous women seen at an urban prenatal clinic; sociodemographic factors such as occupation and education did not affect the prevalence. A report from Italy of 1441 asymptomatic pregnant women, representing 30% of all pregnancies in a defined geographic area, found a prevalence of 4.9%.[14]

Screening for BV was not considered by the second U.S. Preventive Services Task Force. This report focuses on randomized controlled trials of BV treatment in pregnancy to examine the effectiveness and harms of treatment.

Methods

Analytic Framework

An analytic framework was developed to outline issues and to focus the literature search (Figure 1). The analytic framework begins with a population of pregnant women asymptomatic for BV who are at average risk (the general population of pregnant women) or high risk for preterm delivery. Women were considered to be at high risk for preterm delivery if they had a previous preterm delivery. 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—the probability of delivery before a certain gestational age—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. As gestational-age–specific neonatal outcomes have improved, preterm delivery prior to 37 weeks has become less important clinically. Preterm delivery before 34 weeks is clinically more important, thus, we were most interested in this outcome. Other outcomes considered were preterm premature rupture of membranes, preterm labor,

spontaneous abortion, postpartum endometritis, and neonatal sepsis.

Using the two populations defined above, the following key questions are addressed in the present study:

- Does treatment of BV reduce adverse pregnancy outcomes in the general population of pregnant women?
- Does treatment of BV reduce adverse pregnancy outcomes in women at high risk for preterm delivery?
- What adverse effects does the treatment of BV have on pregnancy outcomes?

Literature Search Strategy

Studies of screening and treatment of BV in pregnancy were identified from multiple searches in MEDLINE from 1966 to 1999 by using the MeSH terms *bacterial vaginosis, bacterial infections, vaginitis, mass screening, clinical trials, premature labor, premature infant, pregnancy, pregnancy complications, sensitivity and specificity, obstetric surgical procedures,* and *gynecologic surgical procedures,* the Cochrane Controlled Trials Register and Library,[15] reference lists of selected publications, and national experts. Randomized trials of treatment in pregnancy that evaluated pregnancy outcomes in outpatients with BV and provided sufficient data to interpret results were selected for inclusion. Seven randomized controlled trials of BV treatment in pregnancy were included in the final analysis.

Data Analysis and Synthesis

For each study, we measured the effect of treatment by calculating the difference in the rate of a pregnancy outcome in the control group minus the treatment group. This difference, also known as the absolute risk reduction (ARR), can be converted to a number needed to treat by taking its inverse.[16] With the use of STATA software,[17] we applied a stepwise procedure, based on the profile likelihood method[18–21] to assess heterogeneity, to pool studies when appropriate, and to calculate the mean and 90% confidence intervals (CIs). The stepwise procedure can either result in clusters of studies with similar results or one cluster in which all studies have similar results.

To provide a clinical interpretation of the results, estimates derived from the meta-analysis and from a systematic review of studies of screening for BV were used to construct a balance sheet that summarizes the benefits and harms of screening for BV in 1000 high-risk women.[22]

Results

Accuracy of Screening Tests

Two methods for diagnosing BV are the clinical criteria of Amsel et al.[1] and Gram stain. In 1983, Amsel et al.[1] proposed that clinical diagnostic criteria for BV be standardized to three of four of the following: vaginal discharge pH >4.5, homogeneous discharge adherent to the vaginal wall, amine "fishy" odor immediately on mixture of discharge with 10% KOH solution, or clue cells on wet mount.

The reliability of these clinical signs in community practice, especially in obstetric practice, is unknown. Measurement of pH in the vagina varies by whether the sample is taken from a vaginal wall, the vaginal fornix, or the cervical os, with the cervix having a higher pH than the vagina. The specificity of homogeneous discharge in pregnancy has been questioned because many pregnant women experience increased vaginal discharge.[23,24] Clue cells are frequently used in clinical practice (at times as the sole criterion for treatment) because of their high predictive value, but they are subject to interobserver variation.[25] Recently, test kits with simple indicators, such as plus signs for pH >4.5 and presence of amines, have been marketed in attempts to improve reproducibility.

Gram stain of vaginal discharge may be a more reliable means of diagnosing BV and offers the added ability of quantifying and classifying bacterial load.[26,27] For these reasons, Gram stain has been the primary means used to diagnose BV in epidemiologic and treatment studies. Gram stain is often impractical for routine clinical use 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, the question remains as to whether research findings can be directly translated into practice. The preferred diagnostic test would be the one that best predicts pregnancy outcomes.

Two different Gram stain scoring systems[26,27] have been developed and compared with the clinical criteria of Amsel et al.[1] Comparisons of Gram stain by using the criteria of Spiegel et al.[26] have demonstrated sensitivities ranging from 62% to 97% and specificities of 66% to 95%.[23,24] The criteria of Nugent et al.[28] for Gram stain have shown sensitivity of 89% and specificity of 83%. The VIP study examined the interobserver variability among their five study centers and found that the scoring system of Nugent et al.[27] had greater intercenter reliability with Spearman's rank correlation of 0.82 versus 0.61 for Spiegel et al.[26] Consequently, the criteria of Nugent et al.[27] were accepted as the preferred method for Gram stain evaluation.

Eradication and Teratogenicity

Oral metronidazole and oral clindamycin, as well as vaginal metronidazole gel or clindamycin cream, are used to treat BV. In pregnancy, oral metronidazole and oral clindamycin are the recommended regimens, with metronidazole gel as an alternative. According to the Centers for Disease Control and Prevention (CDC), 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.[29] Side effects from oral metronidazole include gastrointestinal upset, nausea, metallic taste, and disul-

firam reaction. The CDC-recommended treatment for BV in pregnancy is 250 mg oral metronidazole three times a day for 7 days.[29] This lower dosage is recommended to minimize exposure to the fetus. Alternative regimens include metronidazole 2 grams single dose or oral clindamycin 300 mg twice a day for 7 days. The CDC does not recommend the use of clindamycin vaginal cream in pregnancy, because two randomized controlled trials suggested an increase in preterm delivery in treated patients.[30,31]

Metronidazole, the most commonly prescribed antibiotic for BV, is effective at altering the abnormal vaginal flora and appears to have no teratogenic effects. A meta-analysis of 10 controlled trials, with a total of 1203 gynecologic patients, found that all oral regimens, whether single dose or full 7-day course, eradicated BV in 85% to 87% of women prior to 4 weeks post-treatment and in 72% to 78% of women at 4-week follow-up.[32] This meta-analysis did not address metronidazole therapy in obstetric patients, for whom investigators speculate that longer courses may be necessary to treat any upper-tract disease. A systematic review of randomized controlled trials of BV treatment in pregnancy found all compared treatments to be effective at eradicating BV.[15] Despite clinicians' initial concerns about prescribing metronidazole in pregnancy, particularly in the first trimester, two meta-analyses of case–control and cohort studies found no evidence for teratogenesis as a result of using metronidazole in pregnancy.[33,34]

Effectiveness of Treatment

Table 1 summarizes results of the seven randomized clinical trials included in this review.[30,31,35–39] The studies varied in diagnostic methods, setting, populations, route, duration, timing, and vehicle of antibiotic therapy. Three trials were conducted at single U.S. universities[30,36,37]; three were multicenter trials: one in the United States,[39] one in Australia,[38] and one in the Netherlands.[35] One study was conducted in a community setting in Indonesia.[31] All studies were systematically reviewed for quality using Jadad criteria and were judged to be of good quality.[40]

Three trials used oral metronidazole alone,[36,38,39] one used oral metronidazole plus erythromycin,[37] and three used intravaginal clindamycin alone.[30,31,35] Five of seven studies measured eradication of BV as judged by negative test results at 4 to 7 weeks post-treatment. Treatment was shown to be effective in eradicating BV in three studies reporting these results.[31,37,39] In three studies, participants were given only one course of treatment.[30,31,36] In two studies,[37,38] women were treated 2 to 4 weeks after initial treatment only if they were BV positive at follow-up screening. In contrast, two studies[35,39] repeated treatment regardless of BV status on follow-up examination. No trial reported sufficient information on neonatal sepsis, endometritis, or spontaneous abortion to allow inclusion of these outcomes in the meta-analysis.

Does treatment of BV reduce adverse pregnancy outcomes in the general population of pregnant women? Four studies reported results of the effect of BV treatment on pregnancy outcomes in average-risk women.[30,31,38,39] None found significant benefit of treatment for any of the pregnancy outcomes studied.

There was no difference between treatment and placebo groups in the rate of preterm delivery at less than 37 weeks (pooled ARR=0.001; 90% CI=−0.017 to 0.019).

No study of average-risk women reported preterm delivery before 34 weeks, and two reported results for preterm delivery before 32 weeks.[31,39] Neither of those studies had a significant effect. The study using vaginal clindamycin[31] had a nonsignificant trend, indicating potential harm of treatment.

Two of three studies of average-risk women reporting rates of preterm premature rupture of membranes showed harm (pooled ARR=−0.014; 90% CI=−0.027 to 0.000),[30,39] and one showed no benefit (ARR=0.017; 90% CI=−0.010 to 0.044).[38]

Three of the four studies reporting low birth weight showed no benefit (pooled ARR=−0.004; 90% CI=−0.020 to 0.013), whereas one[30] suggested harm (ARR= −0.092; 90% CI=−0.176 to −0.008).

There does not appear to be a clinical benefit in terms of pregnancy outcomes to treating asymptomatic BV during the second trimester in the general population.

Does treatment of BV reduce adverse pregnancy outcomes in women at high risk for preterm delivery? Five studies reported results for high-risk patients.[35–39] The earliest of these studies[36] examined the efficacy of oral metronidazole between 16 and 20 weeks of gestation in 80 women who had BV and a previous preterm delivery from either preterm premature rupture of membranes or idiopathic preterm labor. It was conducted in a high-risk obstetric clinic. Patients with symptomatic BV were not explicitly excluded. The next trial[37] included 177 patients from several public health clinics in Jefferson County, Alabama, with BV who had a history of spontaneous preterm delivery. Patients with symptomatic BV were not specifically excluded. The third trial[38] included 34 patients who had BV and a history of spontaneous preterm delivery. It explicitly excluded symptomatic patients. The fourth trial,[39] the National Institute for Child Health and Human Development (NICHD) Maternal–Fetal Network Study, focused exclusively on asymptomatic patients and consisted of 210 patients with BV and a history of spontaneous preterm delivery. The fifth trial[35] included 22 patients with spontaneous preterm delivery in their last pregnancy.

Four studies[36–39] reported results for preterm deliv-

Table 1. Descriptive features and effect sizes of included studies

Study (Jadad 40 score*)	No. completed/ enrolled	Screening methods/ Screening timing (weeks' gestation)	PTD <37 weeks	PTD <34 weeks	PTD <32 weeks	PPROM	LBW <2500 g
				ARR	(90% CI)**		
Average-risk women							
McGregor[30] (3)	129/142	Gram stain + Amsel (16 to 27)	−0.077 (−0.169 to 0.014)			−0.006 (−0.068 to 0.056)	−0.092 (−0.176 to 0.008)
Joesoef[31] (4)	681/745	Gram stain (14 to 26)	−0.015 (−0.059 to 0.029)		−0.021 (−0.044 to 0.003)		−0.021 (−0.056 to 0.012)
McDonald[38] (4)	480/480	Gram stain (16 to 26)				0.0017 (−0.010 to 0.044)	−0.003 (−0.034 to 0.027)
Carey[39] (5)	1919/1953	Gram stain (16 to 23)	0.030 (−0.021 to 0.028)		0.004 (−0.008 to 0.016)	−0.014 (−0.028 to 0.000)	0.005 (−0.019 to 0.029)
High-risk women							
Morales[36] (4)	80/94	Amsel (13 to 20)	0.263 (0.096 to 0.429)	0.066 (−0.035 to 0.166)		0.288 (0.149 to 0.427)	0.197 (0.042 to 0.362)
Hauth[37] (4)	177/177	Amsel (<24)	0.183 (0.052 to 0.314)				
McDonald[38] (4)	34/34	Gram stain (16 to 26)	0.294 (0.082 to 0.507)	0.118 (−0.061 to 0.296)		0.176 (0.024 to 0.329)	0.235 (0.005 to 0.465)
Carey[39] (5)	210/213	Gram stain (16 to 23)	−0.075 (−0.189 to 0.039)	0.012 (−0.055 to 0.078)		−0.036 (−0.101 to 0.030)	−0.040 (−0.137 to 0.057)
Vermeulen[35] (4)	22/22	Gram stain (<26)		0.000 (−0.202 to 0.202)			

*Measures quality of randomized controlled trials on a 5-point scale.
**Negative value indicates that outcome was more common in treated group than in controls (i.e., adverse effect of treatment).
PTD, preterm delivery; PPROM, preterm premature rupture of membranes; LBW, low birth weight; ARR, absolute risk reduction; CI, confidence interval.

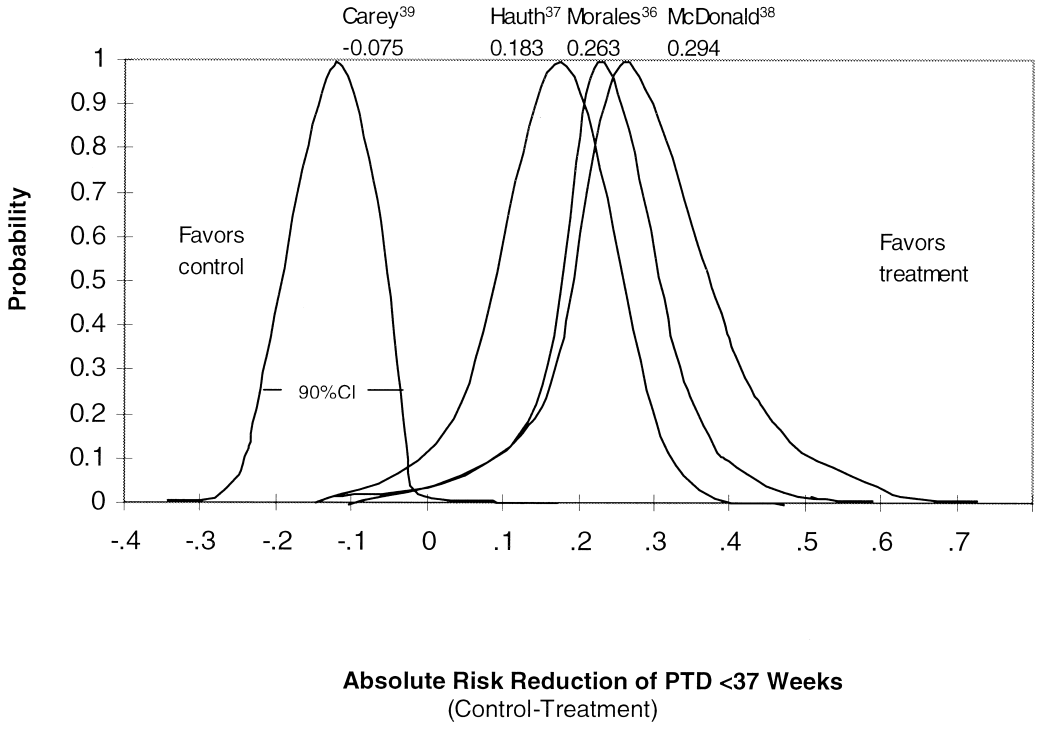

Figure 2. Individual results of four studies reporting rates of preterm delivery (PTD) before 37 weeks in high-risk patients. The measure of effect is a difference in probability of benefit from control minus treatment (absolute risk reduction [ARR]). The width of the curve indicates the precision of the estimate and is used to calculate 90% confidence intervals.

ery less than 37 weeks (Figure 2). Three of these studies were homogeneous and showed benefit (pooled ARR=0.22; 90% CI=0.13 to 0.31),[36–38] indicating 22 fewer preterm deliveries at less than 37 weeks per 100 patients treated (Figure 3). The NICHD trial[39] showed no benefit (ARR=−0.075; 90% CI=−0.189 to 0.039) (Figure 3, curve at left). Two studies provided data for spontaneous preterm delivery before 37 weeks.[37,38] In these studies, the pooled ARR was 0.208 (90% CI=0.096 to 0.321). The smaller study, with a total sample size of 34, showed a stronger benefit.

Four studies reported preterm delivery or spontaneous preterm delivery prior to 34 weeks. None of the four studies showed statistically significant improvement in the treatment group. The study that showed the trend toward greatest benefit with an ARR of 0.118 also had the least precision because of small sample size (17 patients in each group).[38] When pooled, these studies had a slight trend toward benefit that was not statistically significant (pooled ARR=0.036; 90% CI=−0.021 to 0.092) (Figure 4).

Three studies reported results on preterm premature rupture of membranes.[36,38,39] Results from the study by Morales et al.[36] showed the greatest benefit (ARR=0.288; 90% CI=0.149 to 0.427). McDonald et al.[38] reported an ARR of 0.176 (90% CI=0.024 to 0.329), whereas Carey et al.[39] showed no benefit, with an ARR of −0.036 (90% CI=−0.101 to 0.030). Results from studies by McDonald et al.[38] and Morales et al.[36] were sufficiently similar to pool with a pooled ARR of 0.259 (90% CI=0.149 to 0.369). A similar trend across studies was found for low birth weight less than 2500 grams. Three studies reported results on this outcome, with two [36,38] suggesting a benefit to treatment (pooled ARR=0.206; 90% CI=0.078 to 0.335) and one[39] suggesting no benefit (ARR=−0.040; 90% CI=−0.137 to 0.057).

We examined all high-risk studies for factors that could explain variation and possibly define a subgroup of high-risk patients who may benefit from BV treatment (Table 2). The most striking difference was their variation in preterm delivery rates before 37 weeks in the placebo groups. The NICHD study,[39] at 23%, had the lowest rate, followed by McDonald et al.[38] at 35%, Morales et al.[36] at 39%, and Hauth et al.[37] at 57%. It was not possible to calculate the preterm delivery rate for BV patients for the study by Vermeulen and Bruinse,[35] although the preterm delivery rate among the entire high-risk group (with and without BV) was 21%. The results of Carey et al.[39] may have portrayed the experience for "general" high-risk patients, whereas McDonald et al.,[38] Morales et al.,[36] and Hauth et al.[37] might have identified a "more selected" high-risk group that was more likely to benefit from BV treatment. However, the factor that defined this subgroup of high-risk women is not known.

Morales et al.[36] reported benefit of treatment and reported a high proportion of women reporting two or

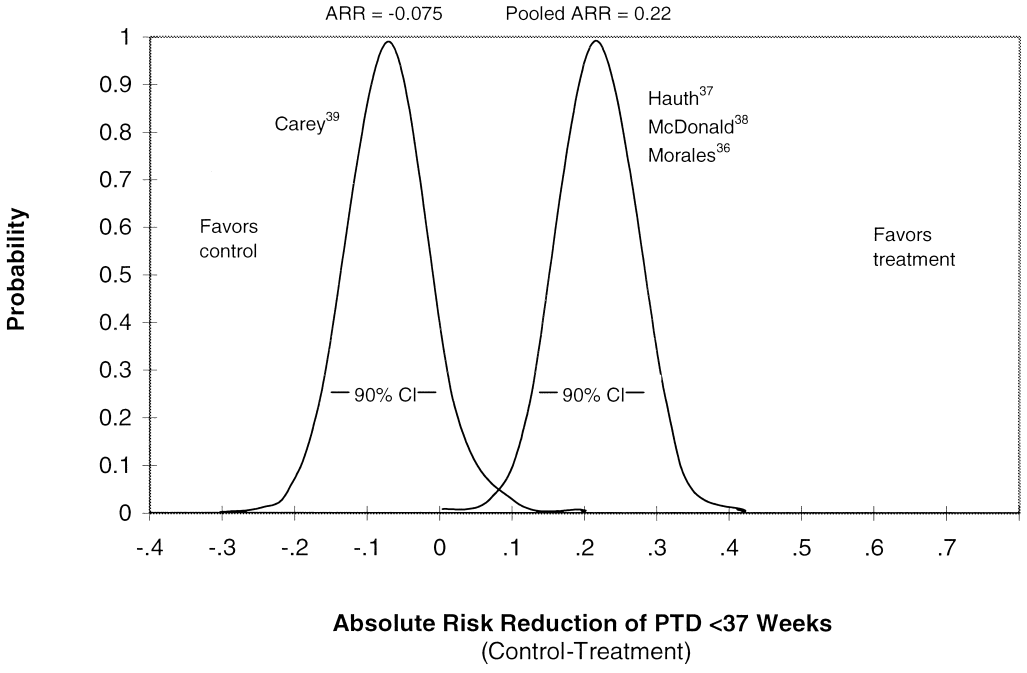

Figure 3. Pooled results of four studies reporting rates of preterm delivery (PTD) before 37 weeks in high-risk patients. The pooled absolute risk reduction for Hauth et al.,[37] McDonald et al.,[38] and Morales et al.[36] was 0.22 (90% CI=013 to 0.31), indicating 22 fewer preterm deliveries before 37 weeks per 100 patients treated. One study, Casey et al.,[39] was dissimilar from the others and did not pool. In that study, the ARR was −0.075 (90% CI=−0.189 to 0.039), indicating seven additional preterm deliveries before 37 weeks per 100 patients treated.

more previous preterm deliveries. Other studies did not provide data on the number of previous preterm deliveries in their populations, so we could not compare them on this factor. Morales et al.[36] also selected for patients who experienced preterm delivery in their last pregnancy, whereas Carey et al.,[39] Hauth et al.,[37] and McDonald et al.[38] asked if patients had ever experienced preterm delivery. The issue of timing and quantity of previous preterm deliveries could be a strong predictor of preterm delivery and should be examined further.

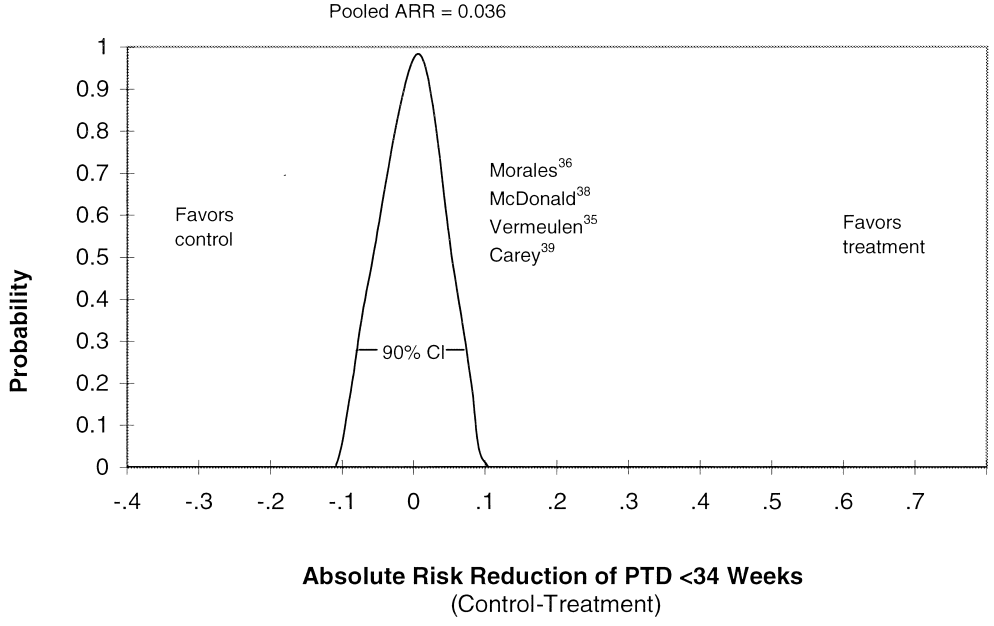

Figure 4. Pooled results of four studies reporting rates of preterm delivery (PTD) before 34 weeks in high-risk patients. None of the four studies reported a statistically significant decrease in preterm delivery before 34 weeks with treatment, and their pooled effect was not statistically different from zero (0.036; 90% CI=−0.021 to 0.092).

Table 2. Overview of high-risk studies

Factor	Carey[39]	McDonald[38]	Hauth[37]	Morales[36]	Vermuelen[35]
PTD <37 weeks, placebo	23%	35%	57%	39%	
GA (wk) at treatment	16–23	24	22–24	13–20	26
Treatment	Oral metronidazole 2 g, repeat @ 48 hr	Oral metronidazole 400 bid, 2 d	Oral metronidazole 250 mg tid, 7 days, plus oral erythromycin 333 mg tid, 14 d	Oral metronidazole 250 mg tid, 7 d	Clindamycin 2% vaginal cream daily, 7 d
Second treatment	All, 24–29 wk	If positive test, 4 wk post-treatment	If positive test, at 28 wk	No second treatment	All, 32 wk

PTD, preterm delivery; GA, gestational age.

There were considerable differences among choice of antibiotic(s), route of administration, duration of therapy, and timing of treatment in pregnancy. Because each study differed in therapeutic regimens, we were unable to determine if these differences explained differences in results.

Timing of treatment before 16 weeks is theorized to be important to the mechanism of BV in preterm delivery. Three studies treated all participants before 20 weeks gestation. Joesoef et al.[31] treated 50% before 20 weeks, and Carey et al.[39] treated 33% before 18 weeks. A study by Alvi and Lamont,[41] published only in abstract form, examined the effect of treatment timing and found a threefold reduction in overall preterm delivery prior to 37 weeks when treatment was administered prior to 16 weeks' gestation. This finding may also be important in defining the population of pregnant women who may benefit from screening for BV.

What adverse effects does the treatment of BV have on pregnancy outcomes? Two studies suggested potential harm of BV treatment, reporting increased rates of preterm delivery before 34 weeks in BV-negative women who received BV treatment. Hauth et al.[37] randomized high-risk patients to BV treatment regardless of BV screening status, resulting in treatment of a subgroup of women without BV. Women without BV who were treated with antibiotics had an increased rate of preterm delivery prior to 34 weeks (13.4%) compared with women without BV who were not given antibiotics (4.8%; $p=0.02$). Similarly, Vermeulen and Bruinse[35] found an increased rate of preterm delivery less than 34 weeks in women without BV who were treated with antibiotics (12.5%) versus women without BV who were not given antibiotics (4.1%). Additionally, Vermeulen and Bruinse[35] reported a statistically significant increase in neonatal sepsis rates in the treated BV-negative group (0% vs 8%; $p<0.05$).

In the NICHD trial,[39] the second treatment could have been given to women who were without BV at the time, but we do not know which of the NICHD patients were BV negative at second treatment. These data emphasize the importance of the accuracy of screening tests to diagnose BV.

Discussion

Summary of Benefits and Harms

In summary, there appears to be no benefit to screening and treating for BV in the general population of pregnant women. The findings for average-risk women are consistent with those of a recent Cochrane review of treatment of BV in pregnancy.[15] We similarly found no benefit to screening all women at high risk for preterm delivery (women with a previous preterm delivery) for the clinically important outcomes of preterm delivery prior to 34 weeks, low birth weight less than 2500 grams, and preterm premature rupture of membranes.

The finding of benefit in some high-risk studies suggests that there may be a subgroup of high-risk women that may benefit from screening for BV in pregnancy. Table 3 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 population. The base case for the general high-risk population incorporates the mean and 90% CIs from the NICHD study[39] for the listed outcomes. The second scenario incorporates the pooled results of three other high-risk studies.[36–38] Of note, all studies used in this balance sheet used metronidazole therapy. In the base case, we assumed that treating these women for BV reduces their risk of adverse pregnancy outcomes to that of BV-negative women (i.e., the maximum plausible effect), as well as a worst-case scenario, using the lower 90% CI of the pooled estimate. In both scenarios we also assumed that metronidazole therapy might be associated with a higher rate of preterm delivery less than 34 weeks in high-risk patients without BV, because the only trial of these four that examined

Table 3. Summary of benefits and harms of screening 1000 high-risk pregnant women for bacterial vaginosis

Benefit and relevant factors	"General" high-risk group[a]	"More selected" high-risk group[b]
Assumptions		
Proportion of pregnant women who meet screening criteria	0.1	0.03
Prevalence of BV in population	0.25	0.25
Relative risk of PTD in BV patients	1.6	1.6
Sensitivity of screening test	0.95	0.95
Specificity of screening test	0.95	0.95
Adherence to treatment	0.8	0.8
Effect sizes, BV patients (probability: control group vs treated group [CI])[c]		
PTD <37 weeks	−0.075 (−0.19 to +0.04)	+0.22 (+0.13 to +0.31)
PPROM	−0.04 (−0.101 to +0.03)	+0.29 (+0.15 to +0.43)
PTD <34 weeks	+0.012 (−0.06 to 0.08)	+0.06 (+0.01 to +0.15)
Effect sizes, patients without BV (probability: control group vs treated group)[c]		
PTD <37 weeks	0	0
PPROM	0	0
PTD <34 weeks	−0.02	−0.06
Results (n)		
Patients with unsuspected BV	250	250
Correctly diagnosed with BV	238	238
BV patients who complete therapy	190	190
BV patients with missed diagnosis	13	13
Incorrectly diagnosed with BV	38	38
Outcomes[c]		
Decrease or increase in PTD <37 weeks (CI)	−14 (−36 to +7)	+42 (+25 to +59)
Decrease or increase in PPROM	−8 (−19 to +4)	+49 (+28 to +70)
Decrease or increase in PTD <34 weeks	+2 (−11 to +14)	+9 (−2 to +19)

[a]Screen all women who have at least one previous PTD.
[b]Screen if there is more than one previous PTD or other risk factors.
[c]Minus sign indicates a net increase, plus indicates a net decrease, in adverse effects.
BV, bacterial vaginosis; PTD, preterm delivery; CI, confidence interval; PPROM, preterm premature rupture of membranes.

this effect found a clinically and statistically significant harmful effect.[37] 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 14 additional preterm deliveries before 37 weeks (90% CI=7 fewer to 36 additional cases), 8 additional cases of preterm premature rupture of membranes (90% CI=4 fewer to 19 additional cases), and 2 fewer preterm deliveries before 34 weeks (90% CI=14 fewer to 11 additional cases).

In the second high-risk group, screening and treatment results in 42 fewer preterm deliveries before 37 weeks (90% CI=25 to 59), 49 fewer cases of preterm premature rupture of membranes (90% CI=28 to 70), and 9 fewer cases (90% CI=19 fewer to 2 additional cases) of preterm delivery before 34 weeks per 1000 women screened. One case of preterm delivery at less than 34 weeks would be prevented for every 111 patients screened; likewise, one case of preterm delivery at less than 37 weeks would be prevented for every 24 (90% CI=17 to 40) patients screened. Because we assumed a potential increase in preterm delivery before 34 weeks in BV-negative patients, 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).

Generalizability

There are several issues of generalizability to consider to determine whether screening and treating for BV may be useful for patients. First, all U.S. studies were conducted in tertiary referral centers or public health clinics and may not be generalizable to community-based practices. Second, screening methods used in research studies may not reflect those employed in everyday practice. One technique frequently used in clinical practice is screening by identification of clue cells alone. There are no studies of BV treatment that have looked at the effectiveness of treatment in women who have been identified as having BV by this criterion alone. Third, we defined patients as asymptomatic if they were most likely identified through routine prenatal care and were not presenting for evaluation of BV symptoms. However, the details for identification of

patients were not explicitly stated in two studies.[36,37] Consequently, it is possible that women presenting for evaluation of BV symptoms were also included. The women with symptomatic BV may represent a different risk category for adverse pregnancy outcomes.

Recommendations for Future Research

Further characterization of the population most likely to benefit, if any, is needed. In addition, the optimum timing of screening and treatment to determine the effect of treatment regimens on pregnancy outcomes needs investigation. Particular attention should be paid to the potential adverse effects of treating BV in pregnancy.

Because epidemiologic studies typically use the Gram stain as the diagnostic standard and clinicians typically use clinical criteria, translation of findings from research to clinical practice is of special concern. The development of screening and diagnostic tests that can be used in both research and clinical settings should be a high priority. Published trials are heterogeneous in study size, setting, population, demographics, risk factor assessment, screening methods, and treatment protocols, leading to further concerns about the generalizability of published evidence to clinical practice. Studies that use standard diagnostic criteria and treatment protocols in typical practice settings should be conducted, perhaps using networks of clinical practices. Finally, the timing of screening and treatment needs to be more thoroughly studied, given current evidence suggesting that early screening and treatment may be more effective than late.

This study was conducted by the Oregon Health Sciences University Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (Contract No. 290-97-0018), Rockville, MD.

This article is based on a more comprehensive Systematic Evidence Review, which is available online at www.ahrq.gov/clinic/prevenix.htm. That document was reviewed by content experts, including Sharon Hillier, PhD, University of Pittsburgh, Mark Klebanoff, MD, MPH, National Institute of Child Health & Human Development, National Institutes of Health, and Rick Sweet, MD, University of Pittsburgh; by professional organizations, including the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and the American College of Physicians/American Society of Internal Medicine; and public health organizations, including the Canadian Task Force on Preventive Health Care; the National Institute of Child Health & Human Development; the National Institutes of Health; the Centers for Disease Control and Prevention; and the U.S. Navy Bureau of Medicine and Surgery. Review by these individuals and groups does not necessarily imply endorsement of this article or of the accompanying recommendations of the U.S. Preventive Services Task Force.

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