Bacterial Vaginosis in Pregnancy and the Risk of Prematurity

A Meta-Analysis

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OBJECTIVE. We conducted this meta-analysis to determine the magnitude of risk conferred by bacterial vaginosis during pregnancy on preterm delivery.

SEARCH STRATEGY. We selected articles from a combination of the results of a MEDLINE search (1966-1996), a manual search of bibliographies, and contact with leading researchers.

SELECTION CRITERIA. We included case control and cohort studies evaluating the risk of preterm delivery, low birth weight, preterm premature rupture of membranes, or preterm labor for pregnant women who had bacterial vaginosis and those who did not.

DATA COLLECTION AND ANALYSIS. Two investigators independently conducted literature searches, applied inclusion criteria, performed data extraction, and critically appraised included studies. Summary estimates of risk were calculated as odds ratios (ORs) using the fixed and random effects models.

MAIN RESULTS. We included 19 studies in the final analysis. Bacterial vaginosis during pregnancy was associated with a statistically significant increased risk for all outcomes evaluated. In the subanalyses for preterm delivery, bacterial vaginosis remained a significant risk factor. Pooling adjusted ORs yielded a 60% increased risk of preterm delivery given the presence of bacterial vaginosis.

CONCLUSIONS. Bacterial vaginosis is an important risk factor for prematurity and pregnancy morbidity. Further studies will help clarify the benefits of treating bacterial vaginosis and the potential role of screening during pregnancy.

KEY WORDS. Vaginosis, bacterial; gardnerella; infant, premature; meta-analysis. *(J Fam Pract 1999; 48:885-892)*

CLINICAL QUESTION What is the association between bacterial vaginosis and preterm delivery?

Prematurity, whether defined by gestational age or birth weight, increases the risk of neonatal morbidity and mortality, as well as early childhood morbidity. Preterm birth, defined as delivery before 37 weeks' gestation, accounts for 8% to 10% of all births[1] and leads to nearly 75% of all neonatal mortality and 50% of all long-term neurologic damage in children.[2] On average, first-year medical costs for infants born weighing less than 2500 grams exceed that of a full-term infant by $15,000.[3]

Between 25% and 60% of preterm births are thought to be attributable to maternal infections,[4,5] and are thus considered preventable. Bacterial vaginosis (BV) has been suggested as one potentially treatable risk factor for preterm delivery. BV is fairly common, with a prevalence ranging from 10% to 30% in a typical obstetric population[6] to more than 50% in some high-risk groups.[7]

Although otherwise thought to be a fairly benign condition, in pregnancy BV is estimated to confer a two- to threefold increased risk of prematurity.[4,8] Yet the relative risks from the literature range from 0[9,10] to 6.9.[11] These variations may be attributable to differences in study design, sample size, or confounders. The purpose of our meta-analysis was to estimate the magnitude of risk that BV poses on prematurity and pregnancy complications that may lead to prematurity.

Please see accompanying commentary on page 897.

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METHODS

Data Sources

To identify potential studies for inclusion, 2 independent investigators (CF and AH) conducted a MEDLINE search (1966-1996), using the terms "bacterial vaginosis," "gardnerella" and "prematurity," " labor-premature onset," "rupture of membranes-premature," "preterm delivery," or "preterm infant" as both medical subject headings and text words. The bibliographies of obstetric texts, all included studies, relevant reviews, and the Cochrane Library were also reviewed. Finally, we contacted several authors who had published articles on the subject in an attempt to identify any unpublished data.

Study Selection

Studies were included if they met the following criteria: (1) the population studied was pregnant women; (2) the risk

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factor considered was the presence of BV; (3) the outcomes measured included either gestational age or birth weight; secondary outcomes considered were preterm premature rupture of membranes and preterm onset of labor; and (4) study design was either case control or cohort; trials evaluating the benefit of treating BV in pregnancy were included if sufficient data were available to compare the outcomes of those women who had BV with those who did not in the control cohort. Inclusion criteria were applied independently by the 2 investigators; differences were settled by consensus.

Non–English language papers and those containing duplication of previous data were excluded. For articles in which the data presentation prohibited the linking of BV to the outcomes of interest, we contacted the authors in writing for the original data. If the original data were unavailable, we excluded the study from final analysis.

Data Extraction

The same 2 investigators also independently performed data extraction. Disagreements were settled by discussion and consensus.

The population data we collected included country, medical setting, and baseline risk of prematurity. We recorded inclusion and exclusion criteria, but those factors were insufficient to categorize the study population as either high, normal, or low risk. Therefore, baseline risk was determined by calculating the incidence of preterm delivery in the control group for each study. Since the standard incidence of preterm delivery is 8% to 10%, we considered as high risk those studies with rates greater than 10% in the non-BV group; those below were categorized as low or normal risk.

We recorded the method and timing of BV diagnosis. In studies with multiple methods of determining BV, we collected the results for each method. The Gram's stain/wet mount result was preferentially used in the final analysis, as this is the most relevant technique for clinical assessment of BV. Vaginal culture data could only be correlated to outcome by individual microbes, so we limited data recording to *Gardnerella vaginalis* only. We recorded the timing of the diagnosis of BV as presented (ie, weeks of gestational age, trimester, during labor), then grouped the data by trimester. If more than one sample was collected in an individual study, we recorded all results but used the earliest in the analysis.

We recorded outcome data dichotomously in 2 x 2 tables for all 4 study outcomes. Extracted information on the handling of confounding included the method used, the adjusted odds ratio with confidence interval, and the variables included in the final model.

In studies that reported preterm delivery results at multiple gestational age cutoffs, we used only the 37-week cutoff. If studies used a definition other than 37 weeks, their data were noted for subanalysis. Some case control studies defined cases as women in preterm labor but reported data separately from those women who delivered prematurely from those that delivered after 37 weeks. For the preterm delivery outcome, the preterm labor cases who delivered at term were included in the control group.

Validity Assessment

We used validity assessment worksheets that were developed specifically for this project using a summary of previously published criteria.[12-14] Each included study was critically appraised independently by the 2 investigators, and their assessments were compared. A third investigator (LM) settled disagreements. We did not use validity criteria to exclude any study from analysis.

Data Synthesis

We calculated summary estimates of risk as odds ratios using both the fixed and random effects models.[15-17] Additionally, we combined cohort studies to generate summary relative risk estimates using both models. Precision is reported as 95% confidence intervals for each statistic. These calculations were generated using Review Manager 3.0 software.[18] We evaluated homogeneity using the chi-square statistic:[15] the greater the *P* value, the more homogeneous the studies.

We conducted subanalyses by study design, baseline population risk of prematurity, method and timing of BV diagnosis, and country of study population. When the subgroupings resulted in any category having fewer than 3 studies, we did not calculate a summary statistic for that group. We excluded those studies and generated a new pooled risk assessment for the alternate groups only.

To address the issue of confounders, we used the general variance-based model[15,19,20] to combine the adjusted odds ratios of individual studies into a summary odds ratio with its 95% confidence interval.

RESULTS

Data Sources and Study Selection

Our literature review identified 233 studies; no unpublished data were discovered. Reviewing the abstracts identified 39 studies for possible inclusion (27 observational studies and 12 trials). We excluded 11 observational studies because they had an inadequate or no control group (2),[21,22] no vaginal assessment of BV (2),[23,24] repeated data (1),[25] or the inability to link BV with pregnancy outcomes (6).[9,26-30] Nine of the 12 trials did not present their control group cohort data in a way that distinguished the outcomes by the presence or absence of BV and were therefore excluded.[31-39] We included 19 studies[10,11,40-56] in the final analysis: 8 case control trials and 11 cohort studies. Three from this latter group consisted of the placebo group of randomized controlled trials.

We estimated the likelihood of publication bias by generating a funnel plot.[15] The graph of study size versus the logarithm of the ratio results, although funnel-shaped, is not completely symmetric.* Data from small

studies demonstrating a protective effect of BV in pregnancy are missing.

Data Extraction

Twelve of the 19 included studies drew patients from a university or tertiary care hospital setting; the 7 others were clinic based (Table 1). Two studies were conducted in nonindustrialized countries (Nairobi and Indonesia). The remaining studies were performed in the United States (11), Australia (3), the United Kingdom (1), Sweden (1), and Finland (1). The baseline prevalence of preterm delivery ranged from 1.1% to 64.9%, with a mean of 20.0% and a median of 13.8%.

To diagnose bacterial vaginosis, 13 studies used Gram's stain alone or in combination with a wet mount, 2 used gas-liquid chromatography, and 4 used vaginal swab cultures. The timing of risk factor detection varied among the studies, ranging from the first prenatal visit to the time of labor. We grouped the studies by trimester as precisely as possible, resulting in 10 studies diagnosing BV in the first or second trimester, 4 with second or third trimester assessment, and 4 studies discovering BV in the third trimester only (which in most cases was at the time of labor).

In most studies, gestational age was determined by the best obstetric clinical estimate — using the date of the mother's last menstrual period, detection of fetal heart tones, fundal heights, and obstetric ultrasound. In one study, gestational age was determined only by pediatric assessment. Preterm delivery was evaluated as a dichotomous outcome in 18 of the 19 included studies. Two studies used 35 weeks' gestation or less to define a preterm infant; one study used 36 weeks. All others adhered to the standard definition of preterm as any gestation with a duration of less than 37 weeks. Low birth weight was defined as an infant weighing less than 2500 grams at birth in all 6 studies that reported this outcome.

Of the 7 studies evaluating preterm premature rupture of membranes, 2 used 36 weeks as the cutoff for preterm; the other 5 used 37 weeks. Only 2 studies reported the method to determine membrane rupture (both used pH and ferning criteria). The time from rupture of membranes to labor onset varied from 1 to 6 hours in the 4 studies

*This figure is available on the *Journal's* Web site at www.jfampract.com.

TABLE 1

Characteristics of Studies Included in Our Meta-Analysis

Reference	Study Design	Hospital or Clinic Based	Country	Preterm Delivery in Non-BV Group, %	Method of BV Diagnosis	Timing of BV Diagnosis	Outcomes Measured
Elliot et al, 1990	Case control	Hospital	Nairobi	52.5	GS	Third trimester	GA/BW, PPROM
Eschenbach et al, 1984	Case control	Hospital	USA	25	GLC	Third trimester	GA/BW
Gravett et al, 1986	Cohort	Hospital	USA	NA	GLC	Second and third trimester	BW, PPROM, POL
Hauth et al, 1995	Cohort (RCT)	Clinic	USA	25	WM/GS	22-28 weeks	GA
Hay et al, 1994	Cohort	Clinic	UK	2.9	GS	9-24 weeks	GA
Hillier et al, 1988	Case control	Hospital	USA	31.8	GS for GA	20-36 weeks	GA, POL
Hillier et al, 1995	Cohort	Clinic	USA	4.2	GS	23-26 weeks	GA, BW; adj PTD
Holst et al, 1994	Case control	Hospital	Sweden	18.3	WM/GS	23-35 weeks	GA, BW
Krohn et al, 1991	Cohort	Hospital	USA	64.9	VC	Third trimester	GA
Kurki et al, 1992	Cohort	Clinic	Finland	1.1	GS	8-17 weeks	GA, PPROM, POL
Martius et al, 1988	Case control	Hospital	USA	25.5	GS	20-36 weeks	GA, POL; adj PTD
McDonald et al, 1991	Case control	Hospital	Australia	10.7	VC	Third trimester	GA, PPROM, POL; adj PTD
McDonald et al, 1992	Case control	Hospital	Australia	15.8	VC	22-28 weeks	GA,PPROM; adj PTD
McDonald et al, 1994	Case control	Hospital	Australia	41.5	VC	22-28 weeks	GA,POL
McGregor et al, 1990	Cohort	Clinic	USA	2.7	GS	24 weeks	GA, POL
McGregor et al, 1994	Cohort (RCT)	Hospital	USA	3.3	WM/GS	16-27 weeks	GA, BW, PPROM, POL
McGregor et al, 1995	Cohort (RCT)	Hospital	USA	9.7	WM/GS	1st PN visit	GA, PPROM; adj PTD
Meis et al, 1995	Cohort	Clinic	USA	3.1	GS	~24 weeks	GA; adj PTD
Riduan et al, 1993	Cohort	Clinic	Indonesia	11.8	WM/GS	16-20 weeks	GA; adj PTD

PTD denotes preterm delivery; BV, bacterial vaginosis; WM, wet mount; GA, gestational age; adj PTD, confounder-adjusted odds ratio for preterm delivery; GS, Gram's stain; BW, birth weight; GLC, gas-liquid chromotography; PPROM, preterm premature rupture of membranes; VC, vaginal culture; POL, premature onset of labor; RCT, randomized controlled trial.

defining this period.

For the outcome of preterm onset of labor, all 9 studies defined preterm as gestational age less than 37 weeks. Most studies defined labor as regular painful uterine contractions; only 2 required cervical change. Two others considered treatment for preterm labor as the definition of preterm onset of labor.

Validity Assessment

Details about validity assessment and the effect of biases on the summary estimates of individual studies are available elsewhere.* Two biases were common. First was the misclassification of either the predictor or the outcomes, which tended to underestimate risk. Second was the issue of confounding variables, which tended to overestimate the odds ratio.

Data Synthesis

Table 3 shows that women with BV were more likely to deliver a preterm infant (odds ratio, fixed effects model [OR_{FIXED}] 1.85; 95% CI, 1.62-2.11) or an infant weighing less than 2500 grams (OR_{FIXED} 1.57; 95% CI, 1.32-1.87). For the secondary outcomes of preterm premature rupture of membranes and preterm onset of labor, the resultant ORs_{FIXED} were 1.83 (95% CI, 1.39-2.44) and 2.19 (95% CI, 1.73-2.76), respectively. The studies combined for preterm onset of labor met statistical requirements of homogeneity ($P > .25$); those for preterm delivery, low birth weight, and preterm premature rupture of membranes did not. Recalculation of the odds ratio using the random effects model did not result in the loss of statistical significance for any of the main outcomes (Table 2).

Pooling only cohort studies to generate a summary relative risk also resulted in a persistently elevated risk of prematurity for those mothers with BV, ranging from a 1.44- to a 2.86-fold increase (Table 3), and homogeneity criteria were met for low birth weight, preterm premature rupture of membranes, and preterm onset of labor, ($P > .33$) but not for preterm delivery. BV was significantly associated with preterm delivery in nearly all the subanalyses conducted (Table 4).

Seven of the 18 studies evaluating preterm delivery did not perform regression analysis to evaluate for confounding; 4 others did this analysis but did not report an adjusted risk for BV. Thus, only 7 studies had controlled data available for a summary estimate. These studies, with their respective adjusted odds ratios and confounders considered, are listed in Table 5. As expected, the resultant summary estimate of the adjusted odds ratio was lower than that obtained from unadjusted data but remained significant clinically (OR = 1.60), as well as statistically (95% CI, 1.44-1.74).

DISCUSSION

Our study pooled data representing more than 17,000 patients, and the results show BV to be a significant risk factor for preterm and low birth weight deliveries. Additionally, BV is significantly associated with preterm onset of labor and preterm premature rupture of membranes. Summary relative risks calculated using cohort data only, although lower than the odds ratios, also showed a significant association between BV and all prematurity outcomes. Although often used interchangeably with relative risks, odds ratios tend to overestimate risk in cases of a positive association and a nonrare outcome. In our study, odds ratios exceeded relative risks for 3 of the 4 outcomes. This may reflect violation of the rare disease assumption or may simply be due to pooling a different subset of studies.

We believe the nearly twofold increase in prematurity with BV is especially robust for several reasons. First, the results are statistically significant regardless of the statistics used to generate them: odds ratio or relative risk, fixed

*Details are available at www.jfampract.com.

TABLE 2

Summary Ratios for Each Outcome

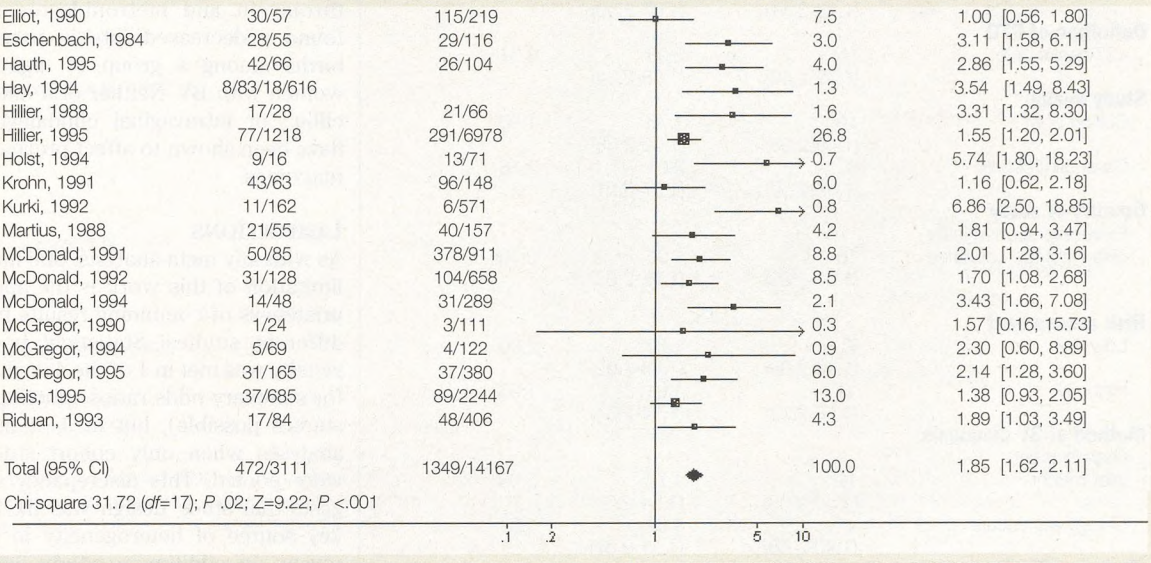
Outcome	No. of Studies	OR FIXED (95% CI)	OR RANDOM (95% CI)	No. of Cohort Studies	RR FIXED (95% CI)	RR RANDOM (95% CI)
Preterm delivery	18	1.85 (1.62-2.11)	2.05 (1.67-2.50)	10	1.56 (1.37-1.78)	1.75 (1.34-2.29)
Low birth weight	6	1.57 (1.32-1.87)	1.73 (1.11-2.69)	3	1.44 (1.21-1.72)	1.43 (1.10-1.87)
Preterm premature rupture of membranes	7	1.83 (1.39-2.44)	2.00 (1.24-3.24)	4	2.74 (1.86-4.05)	2.86 (1.74-4.72)
Premature onset of labor	9	2.19 (1.73-2.76)	2.21 (1.75-2.79)	4	1.92 (1.43-2.58)	1.95 (1.45-2.62)

OR denotes odds ratio; FIXED, fixed effects model calculation; RANDOM, random effects model calculation; CI, confidence interval; RR, relative risk (includes only cohort studies).

TABLE 3

Summary of Included Studies and Pooled Fixed Effect Odds Ratios for the Outcome of Preterm Delivery

Study	Treatment n/N	Control n/N	OR (95%CI fixed)	Weight %	OR (95%CI fixed)
Elliot, 1990	30/57	115/219		7.5	1.00 [0.56, 1.80]
Eschenbach, 1984	28/55	29/116		3.0	3.11 [1.58, 6.11]
Hauth, 1995	42/66	26/104		4.0	2.86 [1.55, 5.29]
Hay, 1994	8/83/18/616			1.3	3.54 [1.49, 8.43]
Hillier, 1988	17/28	21/66		1.6	3.31 [1.32, 8.30]
Hillier, 1995	77/1218	291/6978		26.8	1.55 [1.20, 2.01]
Holst, 1994	9/16	13/71		0.7	5.74 [1.80, 18.23]
Krohn, 1991	43/63	96/148		6.0	1.16 [0.62, 2.18]
Kurki, 1992	11/162	6/571		0.8	6.86 [2.50, 18.85]
Martius, 1988	21/55	40/157		4.2	1.81 [0.94, 3.47]
McDonald, 1991	50/85	378/911		8.8	2.01 [1.28, 3.16]
McDonald, 1992	31/128	104/658		8.5	1.70 [1.08, 2.68]
McDonald, 1994	14/48	31/289		2.1	3.43 [1.66, 7.08]
McGregor, 1990	1/24	3/111		0.3	1.57 [0.16, 15.73]
McGregor, 1994	5/69	4/122		0.9	2.30 [0.60, 8.89]
McGregor, 1995	31/165	37/380		6.0	2.14 [1.28, 3.60]
Meis, 1995	37/685	89/2244		13.0	1.38 [0.93, 2.05]
Riduan, 1993	17/84	48/406		4.3	1.89 [1.03, 3.49]
Total (95% CI)	472/3111	1349/14167		100.0	1.85 [1.62, 2.11]
Chi-square 31.72 (*df*=17); *P* .02; Z=9.22; *P* <.001					



Note: Similar figures for other outcomes are available at www.jfampract.com.
BV denotes bacterial vaginosis.

or random effects models.

Second, decisions regarding data handling in our study were made to produce the most conservative estimate of association. For example, in case control studies that defined cases by the presence of preterm labor, those women with preterm onset of labor who gave birth at term were analyzed with the control group in the preterm delivery analysis. These women may be more likely to have BV, and moving them to the control group for the purpose of analysis would tend to underestimate the risk. In addition, for studies using vaginal cultures for diagnosing BV, we extracted data only for *G vaginalis* culture, which might lead to overdiagnosis, since the presence of *G vaginalis* can be a normal finding. This nondifferential error, as well as the potential imprecision of clinical estimates of gestational age, would tend to bias the summary estimate toward the null. Despite these potential underestimations, BV remained a significant risk factor for prematurity.

Finally, BV remained a significant risk for preterm delivery regardless of the subanalysis groupings. Pooling data from different populations with variable baseline risk or in different settings may lend confidence to the generalizability of these estimates. Caution is warranted, however, when drawing conclusions from any specific subanalysis.

All studies included in this analysis were observational in design, which raises 2 particular concerns: causality and confounding. Because neither the Mantel-Haenszel or DerSimonian and Laird methods for pooling risk estimates can incorporate confounding, we calculated separately the adjusted odds ratio pooled from risk estimates generated by regression analyses in individual studies. This summary of adjusted odds ratios still demonstrated a statistically significant elevated risk of 1.6 for preterm delivery in women with BV. This value may be overestimated, because 4 studies did not report regression results for the variable of BV. Presumably, these values were near the null but were likely not statistically significant, or they would have been reported. A lower summary adjusted odds ratio may have resulted were inclusion of these results possible.

Although causality cannot be proved by observational studies or by meta-analytic combination of such studies, several of the criteria suggesting causality are met.[57,58] The strength of the association is relatively small, ranging from 1.4 to 2.4. Although it is possible that confounders account for all this association, we think that is unlikely given that the controlled summary odds ratio remained significant. This meta-analysis did not address the dose response question directly, although some individual studies reported a stronger association with prematurity outcomes for those who had heavier colonization or higher BV scores. In all but one study this risk factor preceded the outcome, although in some cases

TABLE 4

Summary Odds Ratios for Preterm Delivery Outcome by Subanalyses Groupings

Subanalyses	No. of Studies	OR FIXED (95% CI)	OR RANDOM (95% CI)
Overall	18 (1.62-2.11)	1.85 (1.67-2.50)	2.05
Definition of PTD			
<37weeks only	15 (1.79-2.40)	2.08 (1.88-2.84)	2.31
Study design			
Cohort only	10 (1.49-2.08)	1.76 (1.50-2.56)	1.96
Case control only	8 (1.62-2.50)	2.01 (1.57-3.01)	2.18
Country of study			
Excluding economically disadvantage countries	16 (1.67-2.20)	1.92 (1.75-2.67)	2.16
Risk assessment			
Low risk	7 (1.44-2.09)	1.73 (1.45-2.92)	2.06
High risk	11 (1.58-2.31)	1.91 (1.54-2.54)	1.98
Method of BV diagnosis			
Gram's stain/ Wet mount	12 (1.56-2.08)	1.78 (1.54-2.61)	2.00
G vaginalis culture	4 (1.40-2.38)	1.82 (1.31-2.67)	1.87
Timing of BV diagnosis			
First, second trimester	10 (1.65-2.39)	1.99 (1.65-2.68)	2.10
Second, third trimester	4 (1.40-2.20)	1.76 (1.34-3.63)	2.21
Third trimester	4 (1.21-2.31)	1.67 (0.98-3.45)	1.84

Note: Low risk reflects studies with control group populations whose incidence of preterm delivery was <10%; high risk >10%.
OR denotes odds ratio; FIXED, fixed effects model calculation; RANDOM, random effects model calculation; PTD, preterm delivery; BV, bacterial vaginosis; *G vaginalis, Gardnerella vaginalis.*

vaginal assessment was done at the time of labor. Results are consistent, as can be seen from the summary figures: no study found a protective effect, and only one had a null value. The presence of BV makes biological sense as a contributor to preterm labor and thus to preterm premature rupture of membranes and preterm delivery. One proposed mechanism for this association is the production of phospholipase by the bacteria associated with BV. These enzymes can initiate prostaglandin synthesis, which is one step in the physiology of normal labor activation.[53] Infections in pregnancy are also associated with fetuses that were small for the gestational age,[59] which is another mechanism for low birth weight. Taken together, these factors lend support to a causal association for BV and prematurity.

Identifying BV in pregnancy as a modifiable risk factor for prematurity raises the obvious question of intervention. Accumulating evidence demonstrates that treating pregnant women who have BV with certain oral antibiotics can decrease the risk of prematurity. Clindamycin taken orally by pregnant women with BV decreased preterm deliveries and low birth weight infants by approximately 50%.[38,55] Hauth[42] combined oral erythromycin and metronidazole and found a decreased rate in preterm births among a group of high-risk women with BV. Neither oral amoxicillin[31] or intravaginal clindamycin[33] have been shown to affect pregnancy outcomes.

Limitations

As with any meta-analysis, one major limitation of this work is the appropriateness of combining results from different studies. Statistical homogeneity was met in 1 of the 4 analyses for summary odds ratios (pooling all studies possible), but in 3 of the 4 analyses when only cohort studies were pooled. This discrepancy suggests that study design was likely a key source of heterogeneity in this review. In addition to study design differences, we expected heterogeneity given the range of risks reported in individual studies, the varying population risks, the disparate methods, the timing of BV diagnosis, and the different definitions for the measured outcomes. One method for addressing heterogeneity is to use the random effects model, which accounts for variability between studies when estimating the precision of the risk. When we analyzed the data using this method, none of our conclusions changed.

A second limitation of this project is the possibility of publication bias. Our funnel plot reflects the absence of studies finding that BV protects pregnant women from delivering preterm infants. By chance alone, some studies may find this result, but it is unlikely that such a study would be published. Using Orwin's method[60] to calculate a fail-safe N and our weighted summary effect size of 0.052 (number needed to harm [NNH] = 19), more than 75 studies showing no effect would be needed to drop the risk difference to 0.01 (NNH = 100). Given our systematic and complete search, we think it unlikely that publication bias accounts for our findings, despite the asymmetry of the funnel plot.

Implications for Future Research

The association of BV with prematurity remains at the disease-oriented level of evidence. Although neonatal

TABLE 5

Characteristics of Regression Analyses Evaluating the Association Between Bacterial Vaginitis and Preterm Delivery

Reference	ORadj	95% CI	Factors Adjusted for
Hillier et al, 1995	1.4	1.1-1.8	Age, race, parity, marital status, tobacco, prior LBW, prior early pregnancy loss, CT, NG, trich, GBS
Martius et al, 1988	2.5	1.1-5.0	Age, education, age at first intercourse, PROM, CT, lactobacillus, *U urealyticum*
McDonald et al, 1992	1.8	1.01-3.2	Age, parity, tobacco, substance abuse, prior PTD, prior miscarriage, multiple pregnancy, cervical, incompetence, polyhydramnios, uterine malformations, pyelonephritis, *U urealyticum, M hominus,* Bacteroides spp, Peptostreptococcus spp, GBS, *E coli,* Klebsiella spp, *S aureus,* Haemophilus spp, yeast
McDonald et al, 1991	1.8	1.1-3.1	Age, parity, prior PTD, prior miscarriage, multiple pregnancy, *U urealyticum, M hominus,* Bacteroides spp, Peptostreptococcus spp, GBS, *E coli,* Klebsiella spp, *S aureus,* Haemophilus spp, yeast
McGregor et al, 1995	1.6	1.1-2.4	Age, race, cocaine use, prior PTD, UTI, second or third trimester, bleeding, trich, CT, GBS bacteruria
Meis et al, 1995	1.69	1.04-2.74	Race, parity, tobacco
Riduan et al, 1993	2.0	1.0-3.9	Age, education, tobacco, prior PTD, trich

ORadj denotes adjusted odds ratio; CI, confidence interval; LBW, low body weight; CT denotes Chlamydia trachomatis; NG, Neisseria gonorrhea; GBS, group B steptococcus; trich, trichomonas; PROM, premature rupture of membranes; *U urealyticum, Ureaplasma urealyticum;* spp, species; *M hominus, Mycoplasma hominus; E coli, Escherichia coli; S aureus, Staphylococcus aureus;* PTD, preterm delivery; UTI, upper tract infection.

and infant morbidity and mortality are increased with preterm delivery, the clinical impact of BV or its treatment on these patient-oriented outcomes remains unclear. Additionally, since approximately 50% of the pregnant women with BV are asymptomatic, some advocate universal screening for BV during pregnancy.[61] A large randomized controlled trial evaluating patient-oriented health benefits, as well as costs, is warranted before this becomes a part of routine prenatal care.

RECOMMENDATIONS FOR CLINICAL PRACTICE

BV in pregnancy is associated with a significant risk of preterm delivery. Evidence suggests that oral treatment with certain antibiotics can decrease this risk, especially in those with a previous preterm birth.[62] Thus, if identified during pregnancy, BV should be treated. There is insufficient data to recommend screening for BV during pregnancy.

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