JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Preterm delivery results in adverse outcomes; identifying and treating bacterial vaginosis may reduce its occurrence.

OBJECTIVE To update the evidence on screening and treatment of asymptomatic bacterial vaginosis in pregnancy for the US Preventive Services Task Force.

DATA SOURCES MEDLINE, Cochrane Library, and trial registries through May 29, 2019; bibliographies from retrieved articles, experts, and surveillance of the literature through December 31, 2019.

STUDY SELECTION Fair- or good-quality English-language studies evaluating diagnostic accuracy of tests feasible within primary care; randomized clinical trials (RCTs); nonrandomized controlled intervention studies (for harms only); or meta-analyses of metronidazole or clindamycin.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently assessed titles/abstracts and full-text articles, extracted data, and assessed study quality; when at least 3 similar studies were available, meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, preterm delivery, maternal adverse effects, congenital birth defects, childhood cancer.

RESULTS Forty-four studies (48 publications) were included. No studies evaluated the benefits or harms of screening. Twenty-five studies (n = 15 785) evaluated the accuracy of screening tests; across individual studies and tests, sensitivity ranged from 0.36 to 1.0 and specificity ranged from 0.49 to 1.0. Among trials reporting findings from general obstetric populations (n = 7953), no significant association was observed between treatment and spontaneous delivery before 37 weeks (pooled absolute risk difference [ARD], −1.44% [95% CI, −3.31% to 0.43%]; 8 RCTs, n = 7571) or any delivery before 37 weeks (pooled ARD, 0.20% [95% CI, −1.13% to 1.53%]; 6 RCTs, n = 6307). Among 5 trials reporting findings among women with a prior preterm delivery, findings were inconsistent; 3 showed a significant beneficial effect, while 2 did not. Maternal adverse events from treatment were infrequent and minor (eg, candidiasis) but were slightly more common with active treatment compared with placebo across 8 RCTs. Two meta-analyses of observational studies reported no significant association between metronidazole exposure and congenital malformations (odds ratio, 0.96 [95% CI, 0.75 to 1.22]; odds ratio, 1.08 [95% CI, 0.90 to 1.29]). One cohort study reported no significantly increased incidence of childhood cancer among metronidazole-exposed children (adjusted relative risk, 0.81 [95% CI, 0.41 to 1.59]). However, studies of in utero exposure had important limitations.

CONCLUSIONS AND RELEVANCE Accuracy of screening tests for bacterial vaginosis varies. The evidence suggests no difference in the incidence of preterm delivery and related outcomes from treatment for asymptomatic bacterial vaginosis in a general obstetric population but was inconclusive for women with a prior preterm delivery. Maternal adverse events from treatment appear to be infrequent and minor, but the evidence about harms from in utero exposure was inconclusive.

JAMA. 2020;323(13):1293-1309. doi:10.1001/jama.2020.0233

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Audio and **Supplemental content**

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Bacterial vaginosis is a common lower genital tract syndrome defined as a shift from normal hydrogen peroxide–producing lactobacilli to mixed anaerobes.[1,2] Studies conducted between 1983 and 2006 estimate that only 25% to 50% of women with bacterial vaginosis report symptoms.[3-5] Research has suggested bacterial vaginosis as a risk factor for preterm delivery; a 2007 meta-analysis of 32 studies estimated a pooled odds ratio for the risk of preterm delivery in the presence of asymptomatic bacterial vaginosis of 2.16 (95% CI, 1.56 to 3.00).[6] The causal mechanism is not fully understood.[7,8]

Early identification and treatment of bacterial vaginosis may reduce the incidence of preterm delivery and its associated morbidity and mortality. This review was conducted to inform the US Preventive Services Task Force (USPSTF) for its update of the 2008 recommendation on screening and treatment of bacterial vaginosis in pregnancy to prevent preterm delivery.[9] In 2008, the USPSTF recommended against screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery (D recommendation) and concluded that the evidence was insufficient for asymptomatic pregnant women at high risk for preterm delivery (I statement).

Methods

Scope of the Review

The analytic framework and key questions (KQs) that guided the review are shown in **Figure 1**. Detailed methods, evidence tables, sensitivity analyses, and contextual information are available in the full evidence report at http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/bacterial-vaginosis-in-pregnant-adolescents-and-women-to-prevent-preterm-delivery-screening.

Data Sources and Searches

PubMed, the Cochrane Library, and EMBASE were searched for English-language articles published from January 1, 2006, through May 29, 2019. Because the previous reviews for the USPSTF did not include a systematic search for KQ2 (diagnostic test accuracy), a separate PubMed search from inception through December 31, 2005, was conducted to supplement the main search for this update. ClinicalTrials.gov, the Cochrane Clinical Trials Registry, and the World Health Organization International Clinical Trials Registry Platform were also searched. To supplement systematic electronic searches (eMethods in the Supplement), reference lists of pertinent articles and studies suggested by reviewers were searched. Ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on December 31, 2019.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each KQ (eMethods in the Supplement); disagreements about inclusion were resolved by a third reviewer. Briefly, for KQ1, KQ3, and KQ4, randomized clinical trials (RCTs) and relevant systematic reviews of RCTs, conducted in pregnant women or adolescents, were selected; for KQ1 and KQ3, participants had to be asymptomatic with respect to vaginal symptoms of bacterial vaginosis. For KQ1 and KQ3, studies that compared screening with no screening and reported health outcome benefits (eg, reduction in preterm delivery) or harms (eg, anxiety) were selected. For KQ2, studies that reported on diagnostic test accuracy for Amsel clinical criteria (vaginal pH >4.5, clue cells, discharge, amine odor)[3] or laboratory-based tests in commercial use or feasible for use in primary care settings were selected. Participants were not required to be pregnant in studies selected for KQ2. For KQ4 and KQ5, trials that compared treatment with metronidazole or clindamycin vs placebo or no treatment in symptomatic or asymptomatic pregnant women with bacterial vaginosis and that reported health outcomes related to preterm delivery or other adverse pregnancy outcomes were selected. For KQ5, observational studies that reported on outcomes related to fetal exposure to metronidazole or clindamycin, such as carcinogenesis or congenital malformations, were eligible.

English-language studies that met all study selection criteria, were fair or good methodological quality, and were conducted in countries categorized as very highly developed by the 2017 United Nations Human Development Index were included.[11] Studies included in the prior 2008 review were reassessed against the study selection and methodological quality criteria for this update.

Data Extraction and Quality Assessment

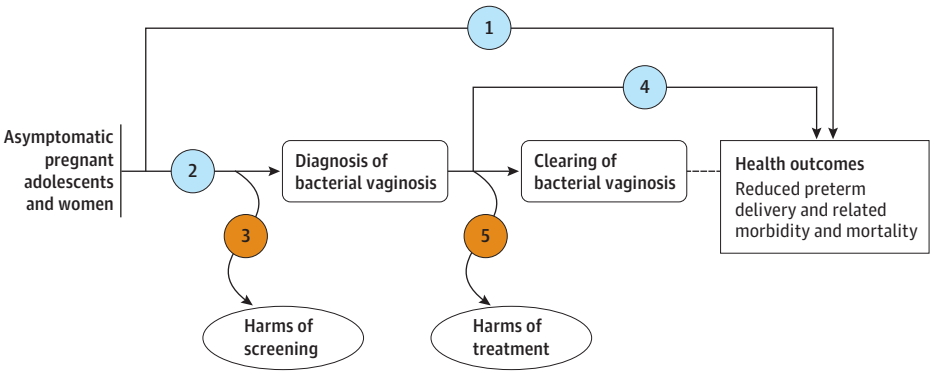
For each included study, 1 reviewer abstracted relevant study characteristics (ie, population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy. Some study authors were contacted to clarify data. Two senior reviewers independently assessed each study's methodological quality using predefined criteria established by the USPSTF (eMethods in the Supplement) and others.[12-16] Disagreements in study quality ratings were resolved through discussion or with an independent assessment from a third senior investigator. Studies reporting multiple outcomes may have been assigned different quality ratings for different outcomes.

Data Synthesis and Analysis

For diagnostic test accuracy (KQ2), data related to sensitivity, specificity, and likelihood ratios were synthesized in tabular and narrative formats. When at least 3 studies using the same index test and test threshold were available, a quantitative synthesis was performed by fitting the bivariate model described by Reitsma et al[17] with the *metandi* package in Stata version 15 (StataCorp) to generate a summary receiver operating characteristics curve and a pooled summary point estimate of sensitivity and specificity. For benefits of treatment (KQ4), findings were synthesized using both absolute risk differences (ARDs) and relative risk (RR) ratios. For harms of treatment (KQ5), odds ratios (ORs) were also used. When a quantitative synthesis was possible, a random-effects model with the inverse-variance weighted method of DerSimonian and Laird with the *metafor* package in R version 2.0-0 (R Foundation for Statistical Computing) was used.[18] Significance testing was based on the exclusion of the null value by the 95% CI around the pooled estimate.

The strength of evidence was assessed based on the Agency for Healthcare Quality and Research *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, which specifies the assessment of study limitations, directness, consistency, precision, and reporting

Figure 1. Analytic Framework: Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery



Key questions

1. Does screening for bacterial vaginosis in asymptomatic pregnant adolescents and women reduce preterm delivery and related morbidity and mortality?
   - a. Does the effect of screening vary by baseline risk (eg, low vs high risk) for preterm delivery?
   - b. Does the effect of screening vary by race/ethnicity?
   - c. Does the effect of screening vary by maternal age?
   - d. Does the effect of screening vary by gestational age?
   - e. Does the effect of screening vary by other risk factors for preterm delivery (eg, co-infection with sexually transmitted infections, HIV status)?
2. What is the diagnostic accuracy of tests used to screen for bacterial vaginosis?
   - a. Does diagnostic accuracy vary by pregnancy status?
3. What are the harms of screening for bacterial vaginosis in asymptomatic pregnant adolescents and women?
4. Does treatment of bacterial vaginosis during pregnancy reduce preterm delivery and related morbidity and mortality?
   - a. Does the effect of treatment vary by baseline risk (eg, low vs. high risk) for preterm delivery?
   - b. Does the effect of treatment vary by race/ethnicity?
   - c. Does the effect of treatment vary by maternal age?
   - d. Does the effect of treatment vary by gestational age?
   - e. Does the effect of treatment vary by other risk factors for preterm delivery (eg, co-infection with sexually transmitted infections, HIV status)?
5. What are the harms of treatment of bacterial vaginosis in pregnant adolescents and women?
   - a. What are the harms of treatment to pregnant adolescents and women?
   - b. What are harms of treatment to the fetus or newborn?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display key questions addressed by the review to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions to outcomes. A dashed line indicates an outcome that precedes subsequent outcomes. Refer to the USPSTF Procedure Manual for further details.[10]

bias for each intervention comparison and major outcome of interest.[19] Two senior reviewers independently developed initial strength of evidence assessments for each relevant outcome and comparison across the KQs; disagreements were resolved through discussion and the independent assessment of a third senior reviewer.

Results

Forty-four studies from 48 publications were included (**Figure 2**). Twenty-five studies of test accuracy (KQ2),[20-44] 13 RCTs evaluating the benefits of treatment with respect to preterm delivery and related pregnancy outcomes (KQ4),[45-57] and 14 studies evaluating the harms of treatment (KQ5)[45,48,49,51,52,55-63] were identified.

Benefits of Screening

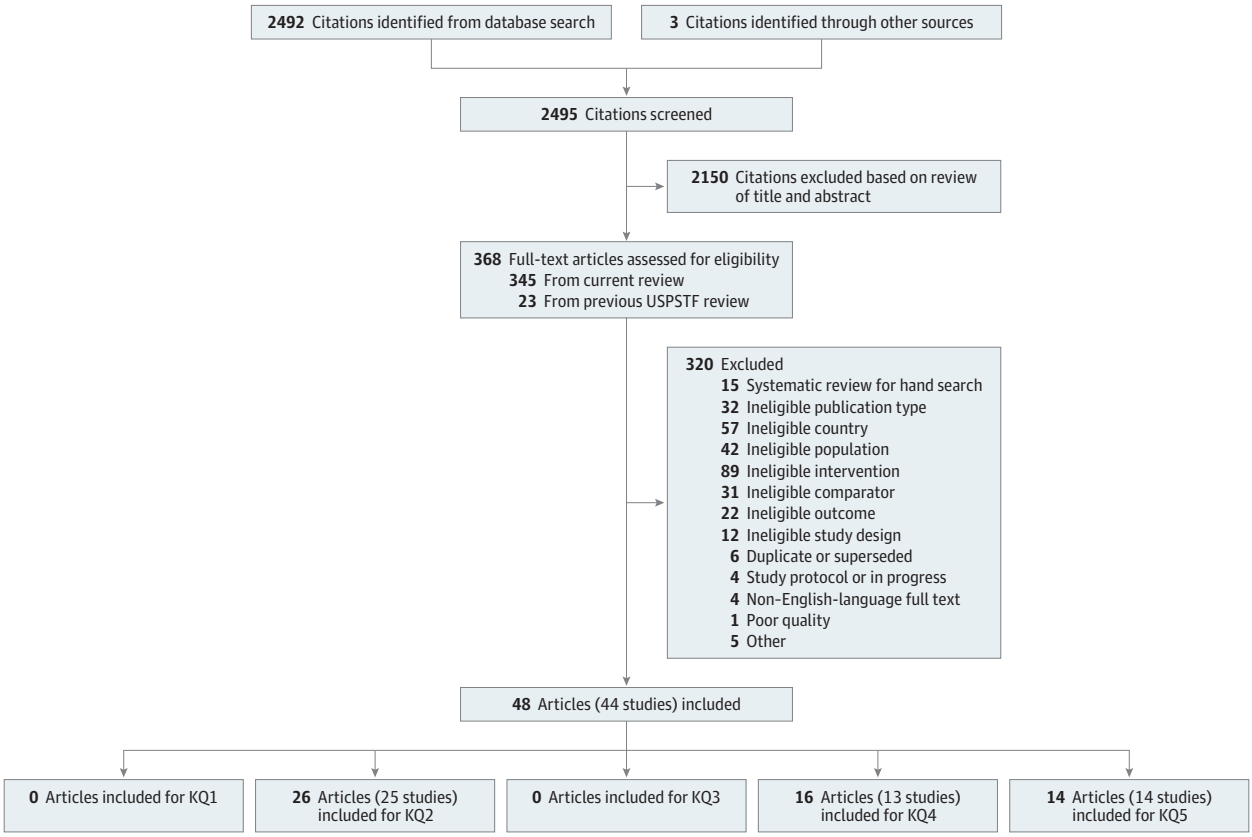
Key Question 1. Does screening for bacterial vaginosis in asymptomatic pregnant adolescent and women reduce preterm delivery and related morbidity and mortality?

No studies were identified.

Accuracy of Screening

Key Question 2. What is the diagnostic accuracy of tests used to screen for bacterial vaginosis?

Figure 2. Literature Search Flow Diagram: Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery



KQ indicates key question; USPSTF, US Preventive Services Task Force.

Table 1. Accuracy of Tests Used for Screening for Bacterial Vaginosis, Compared With Gram Stain Reference Standard

Test	No. of studies/ No. of participants	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
BD Affirm, pooled	5/2936	0.87 (0.80-0.92)	0.81 (0.73-0.88)	4.6 (3.1-6.8)	0.16 (0.11-0.26)
BD Max	1/1338	0.93	0.92	10.9	0.08
BV Blue, range	3/864	0.61-0.92	0.86-0.99	6.3-41.3	0.09-0.14
Complete Amsel clinical criteria[a], pooled	15/7171	0.76 (0.63-0.85)	0.95 (0.89-0.98)	14.1 (6.8-29.2)	0.26 (0.17-0.39)
Modified Amsel clinical criteria[b], pooled	5/2674	0.67 (0.54-0.78)	0.96 (0.93-0.98)	17.3 (10.4-28.8)	0.34 (0.24-0.48)

Abbreviation: LR, likelihood ratio.

[a] Clinical diagnosis is based on the presence of at least 3 of 4 criteria: vaginal pH greater than 4.5, at least 20% of epithelial cells are clue cells on microscopy, amine odor when potassium hydroxide is added to vaginal secretions, thin homogenous discharge.

[b] Similar to complete Amsel criteria except the requirement for thin homogenous discharge is waived. Studies vary with respect to whether all 3 remaining criteria were required or whether 2 of 3 remaining criteria were required.

Twenty-five cross-sectional diagnostic test accuracy studies (n = 15 785) reported test accuracy for laboratory assays and for Amsel clinical criteria (complete or modified). Study characteristics are reported in eTable 1 in the Supplement, and individual study methodological quality is described in eTables 2 through 7 in the Supplement. Six studies were assessed as good methodological quality[23,25,26,31,37,43]; the others were assessed as fair quality generally because of unclear enrollment procedures and unclear information regarding blinding of index and reference test results. The reference standard assessed in nearly all studies was a Gram stain of vaginal secretions, most often interpreted using Nugent criteria, a scoring system based on quantity and morphotypes of organisms present.[64,65] Two studies enrolled exclusively pregnant or asymptomatic women.[23,40] **Table 1** summarizes the accuracy of various tests; across individual studies and tests, sensitivity ranged from 0.36 to 1.0 and specificity ranged from 0.49 to 1.0.

Harms of Screening

Key Question 3. What are the harms of screening for bacterial vaginosis in asymptomatic pregnant adolescents and women?

No studies were identified.

Benefits of Treatment

Key Question 4. Does treatment of bacterial vaginosis during pregnancy reduce preterm delivery and related morbidity and mortality?

Thirteen RCTs (n = 8751) reported findings related to preterm delivery, other pregnancy outcomes, or clearance of bacterial vaginosis.[45-57] Study characteristics are summarized in **Table 2**, with additional characteristics described in eTable 3 in the Supplement. Nine RCTs[45,46,48,50,52,53,55-57] were assessed as good methodological quality, and 4 RCTs[47,49,51,54] were assessed as fair quality, primarily because of concerns related to lack of information on allocation concealment and lack of information to assess adequacy of randomization,[51] lack of treatment blinding,[49,51] post hoc subgroup analyses,[47,49] or lack of intent-to-treat analyses.[54] Individual study methodological quality is described in eTable 4 in the Supplement. No studies reported subgroup findings by maternal or gestational age, race or ethnicity, HIV status, or other population characteristics specified by the KQs.

Four studies were conducted in the US[45,47,53,54]; the others were conducted in Australia[52] and various countries in Europe.[46,48-51,55-57] Ten of the 13 studies (n = 7953) were conducted among general obstetric populations, meaning that patients were enrolled without regard to their risk for preterm delivery.[45,46,48-53,55,56] The percentage of participants with a prior preterm delivery in these studies ranged from 0% to 10.9%. Two of these studies (n = 194) also reported findings among subgroups considered at high risk for preterm delivery because of a prior preterm delivery.[45,52] Three of the 13 studies (n = 279) were conducted solely among participants considered at high risk for preterm delivery.[47,54,57] All 3 defined high risk as a previous preterm delivery; however, 1 study also considered women with a prepregnancy weight less than 50 kg and no previous preterm delivery as high risk.[47] Most studies identified asymptomatic patients during routine prenatal visits and enrolled participants during the second trimester, although criteria for enrollment varied. Three studies enrolled participants without regard to bacterial vaginosis status but reported findings for the subgroup of participants testing positive for bacterial vaginosis at study entry. Study findings are only reported in this article from the subgroups with bacterial vaginosis.[47,49,57]

Three studies evaluated the use of oral metronidazole,[45,52,54] 2 studies evaluated oral clindamycin,[55,56] 1 study evaluated oral metronidazole and erythromycin,[47] and 7 evaluated intravaginal clindamycin.[46,48-51,53,57] The dosages and durations of treatment varied across studies, and most, but not all, used a placebo control. Two studies repeated treatment if the test of a cure demonstrated persistent bacterial vaginosis,[49,52] and 3 studies repeated dosing at a later follow-up point without regard to results from a test of cure for some or all participants.[45,55,57] Twelve of the 13 RCTs[45-56] reported findings related to preterm delivery prior to 37 weeks' gestational age; 1 RCT[57] only reported preterm delivery defined as delivery prior to 34 weeks. Detailed results are summarized in eTable 5 in the Supplement.

Preterm Delivery in General Obstetric Populations

Ten RCTs conducted among general obstetric populations reported preterm delivery outcomes (**Figure 3**). The absolute risk of delivery prior to 37 weeks' gestational age in the placebo groups ranged from 3.1% to 15.7%. Among the 6 studies reporting all-cause preterm delivery, the pooled ARD comparing active treatment with control was 0.20% (95% CI, −1.13% to 1.53%; 6307 participants; I^2 = 0%), and the pooled RR was 1.02 (95% CI, 0.86 to 1.20).[45,46,51-53,55] No individual studies reported a significant difference between active treatment and control. Among the 8 studies reporting spontaneous preterm deliveries, the pooled ARD comparing active treatment with control was −1.44% (95% CI, −3.31% to 0.43%; 7571 participants; I^2 = 61.9%), and the pooled RR was 0.78 (95% CI, 0.56 to 1.07).[45,48-52,55,56] Two of the 8 studies reported statistically significant reductions in spontaneous preterm delivery for active treatment compared with control,[50,56] while the other 6 reported no significant differences between active treatment and control. One of the studies that reported a significant reduction in spontaneous preterm delivery enrolled participants (n = 409) with either bacterial vaginosis or intermediate flora[50]; other population or intervention characteristics that might explain this inconsistency could not be identified.

Three RCTs reported the incidence of preterm delivery prior to 32 weeks' completed gestation among a general obstetric population (eFigures 4 and 5 in the Supplement).[45,51,55] The pooled ARD was −0.30% (95% CI, −0.97% to 0.38%; 5564 participants; I^2 = 15.4%), and the pooled RR was 0.87 (95% CI, 0.54 to 1.42). All 3 studies observed no significant differences between active treatment and control. One RCT also reported no significant difference in preterm delivery at less than 34 weeks' gestation (ARD, −0.04% [95% CI, −2.0% to 1.92%]; RR, 1.0 [95% CI, 0.7 to 1.5]).[45]

Other pregnancy-related outcomes in a general obstetric population for which a pooled summary estimate was calculatable are provided in eFigures 4 and 5 in the Supplement. No significant association between treatment and low birth weight, very low birth weight, or premature rupture of membranes was observed. Studies also reported outcomes for which pooled summary estimates could not be generated, including maternal peripartum infection,[48] stillborn fetus,[49] preterm labor,[53] and neonatal mortality[55]; authors observed no significant differences between active treatment and control for these outcomes.

Preterm Delivery in Women With Prior Preterm Delivery

Five RCTs reported preterm delivery outcomes in this subgroup; 3 reported incidence of preterm delivery at less than 37 weeks,[45,47,52,54] 1 reported incidence of preterm delivery at less than 34 weeks,[57] and 1 reported incidence of preterm delivery at both less than 37 weeks and less than 34 weeks.[39] Findings for this subgroup were not pooled because of heterogenous outcome measures.

In the 4 RCTs (n = 451) conducted among participants with a previous preterm delivery or that reported subgroup findings for such women, the incidence of preterm delivery at less than 37 weeks' gestation in control groups ranged from 22.5% to 57.1% (**Figure 4**).[45,47,52,54] Carey et al[45] and Hauth et al[47] reported all-cause preterm delivery, and Morales et al[54] and McDonald et al[52] reported spontaneous preterm delivery. Three of the 4 RCTs reported a statistically significant favorable treatment effect (ARDs ranging from −18.3% to −29.4%),[47,52,54] while Carey et al[45] (subgroup n = 160) observed no significant treatment effect (ARD, 7.50% [95% CI, −6.09% to 21.09%]). The inconsistency in findings could not be explained based on study or population characteristics (further details are reported in the eResults in the Supplement).

Two RCTs reported the incidence of preterm delivery at less than 34 weeks' gestation among participants with a prior preterm

Table 2. Study Characteristics of Randomized Clinical Trials Reporting Benefits of Treating Bacterial Vaginosis

Source	Country	Study quality	Interventions	No. (%)				Outcomes reported
				With bacterial vaginosis symptoms	Nulliparous	Nonwhite	With prior PTD	
Carey et al,[45] 2000 Andrews et al,[66] 2006	US	Good	Placebo (987 randomized)	0	407 (41.2)	841 (85.2)	110 (11.1)	All-cause and spontaneous PTD <37, 35, and 32 wk Birth weight <2500 and 1500 g Subgroup findings for women with prior PTD; treatment for chlamydia and bacterial vaginosis clearance
			Oral metronidazole (1000 mg dose 4 times on days 0, 2,14, and 16) (966 randomized)	0	436 (45.1)	822 (85.1)	103 (10.7)	
Guaschino et al,[46] 2003	Italy	Fair	No treatment (57 randomized)	0	35 (61.4)	NR	3 (5.3)	All-cause PTD <37 wk Birth weight <2500 g Preterm or term PROM
			Intravaginal clindamycin (2% cream once daily for 7 d) (55 randomized)	0	39 (70.9)	NR	5 (9.1)	
Hauth et al,[47] 1995	US	Fair	Placebo (87)		30 (16)[a]	150 (79)[a]	56 (65.1)[b]	All-cause PTD <37 wk Subgroup findings among women with prior PTD
			Oral metronidazole (750 mg daily for 7 d) and erythromycin (999 mg daily for 14 d) (176 randomized)	NR	84 (19)[a]	309 (71)[a]	121 (70.3)[b]	
Kekki et al,[48] 2001 Kurkinen-Räty et al,[68] 2000	Finland	Good	Placebo (188 randomized)	0	Mean parity 1.9	NR	0	Spontaneous PTD <37 wk Maternal peripartum infection Subgroup findings among participants with clearance of bacterial vaginosis and participants with intermediate flora
			Intravaginal clindamycin (2% cream once daily for 7 d) (187 randomized)	0	Mean parity 1.7	NR	0	
Kiss et al,[49] 2004	Austria	Fair	No treatment (179 randomized)[c]	0	NR (47.8)	NR (2)	Between 33 and 36 wk: 45 (2.1) Between 23 and 32 wk: 24 (1.1)	Spontaneous PTD <37 wk
			Intravaginal clindamycin (2% cream once daily for 6 d) and treatment with oral clindamycin (300 mg twice a day) if still positive at 24 to 27 wk gestation (177 randomized)[c]	0	NR (47.9)		Between 33 and 36 wk: 47 (2.2) Between 23 and 32 wk: 22 (1.1)	
Lamont et al,[50] 2003	UK	Good	Placebo (201 randomized)	0	112 (56)	63 (31)	11 (8)	Spontaneous PTD <37 wk Birth weight <2500 and 1500 g Stillborn fetus
			Intravaginal clindamycin (2% cream once daily for 3 d) (208 randomized)	0	111 (53)	58 (28)	10 (7)	
Larsson et al,[51] 2006	Sweden	Fair	No treatment (411 randomized)	0	187 (45.5)	NR	Among parous women: 13 (6.0)	All-cause PTD <37 wk Spontaneous PTD <37 and <32 completed wk
			Intravaginal clindamycin (2% cream once daily for 7 d) (408 randomized)	0	186 (45.5)	NR	Among parous women: 20 (9.2)	
McDonald et al,[52] 1997	Australia	Good	Placebo (440 randomized)	0	144 (32.7)	53 (12.3)	24 (5.5)	All-cause and spontaneous PTD <37 wk Preterm PROM Subgroup findings for women with prior PTD
			Oral metronidazole (800 mg daily for 2 d) repeated at 28 weeks for women with persistence (439 randomized)	0	139 (31.7)	47 (10.8)	22 (5.0)	

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials Reporting Benefits of Treating Bacterial Vaginosis (continued)

Source	Country	Study quality	Interventions	No. (%)				Outcomes reported
				With bacterial vaginosis symptoms	Nulliparous	Nonwhite	With prior PTD	
McGregor et al,[53] 1994	US	Good	Placebo (69 analyzed)	0	Mean parity, 1.0 (range 0-6)	87 (61.2)	15 (10.9)	All-cause PTD <37 wk Preterm PROM Preterm labor Birth weight <2500 g
			Intravaginal clindamycin (2% cream once daily for 7 d) (60 analyzed)	0				
Morales et al,[54] 1994	US	Fair	Placebo (36 analyzed)	NR	2.2 (1.1)	18 (50)	80 (100)	Spontaneous PTD <37 and 34 wk Preterm labor PROM Birth weight <2500 g
			Oral metronidazole (750 mg daily for 7 d) (44 analyzed)	NR	2.4 (1.2)	20 (45)		
Subtil et al,[55] 2018	France	Good	Placebo (956)	NR	NR	NR	NR	All-cause and spontaneous PTD <37 wk Spontaneous PTD <32 wk Neonatal mortality
			Oral clindamycin (600 mg daily for 4 d or 3 courses [600 mg daily] for 4 d, each 1 mo apart) (1904 randomized)					
Ugwumadu et al,[56] 2003	UK	Good	Placebo (245)[d]	NR	0.8 (1.0)	93 (39)	22 (9)	Spontaneous PTD <37 wk Subgroup findings among participants with intermediate flora
			Oral clindamycin (600 mg daily for 5 d) (249 randomized)[d]	NR	0.8 (1.1)	86 (36)	24 (10)	
Vermeulen and Bruinse,[57] 1999	The Netherlands	Good	Placebo (11)[e]	NR	1.4 (0.9)	NR	11 (100)	All-cause PTD <34 wk Neonatal sepsis
			Intravaginal clindamycin (2% cream once daily for 7 d) at 26 wk and again at 32 wk (11 randomized)[e]	NR	1.6 (0.9)	NR	11 (100)	

Abbreviations: NR, not reported; PROM, premature rupture of membranes; PTD, preterm delivery.

[a] For total study population including those with and without bacterial vaginosis.

[b] For subgroup with bacterial vaginosis.

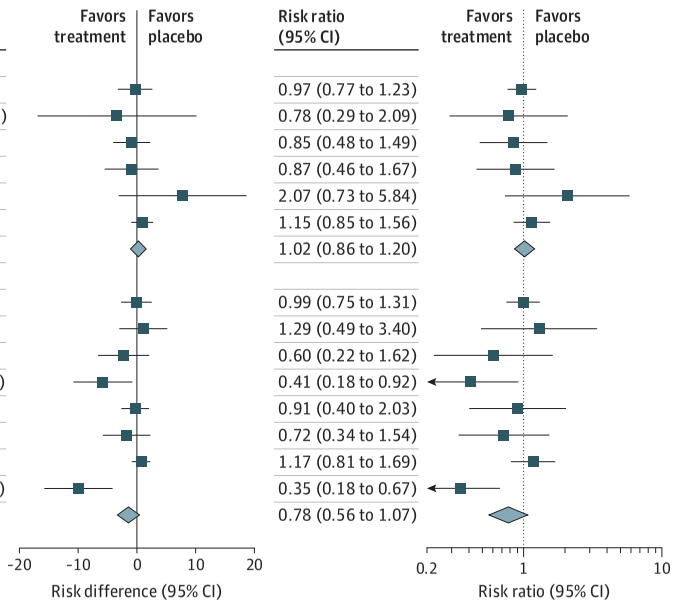
[c] This study randomized a total of 4429 participants to vaginal smear screening, but only a subset of participants tested positive for bacterial vaginosis and received treatment; only data for the bacterial vaginosis–positive subset of the study population was abstracted.

[d] Represents the full randomized population; findings reported only for the subgroup of women with bacterial vaginosis (203 in placebo group; 207 in intervention group).

[e] Represents the number of women with bacterial vaginosis who were randomized to placebo and active treatment; total number randomized was 168 (85 placebo; 83 active treatment).

Figure 3. Effect of Treatment of Bacterial Vaginosis Among the General Obstetric Population

Source	Study quality	No. analyzed	Prior PTD, %	Treatment	Outcome description	Control risk, %	Risk difference (95% CI)	Risk ratio (95% CI)
All-cause preterm delivery								
Carey et al,[45] 2000	Good	1919	10.9	OM	All-cause delivery <37 wk	12.5	-0.35 (-3.30 to 2.59)	0.97 (0.77 to 1.23)
Guaschino et al,[46] 2003	Good	100	7.1	VC	All-cause delivery <37 wk	15.7	-3.44 (-17.00 to 10.12)	0.78 (0.29 to 2.09)
Larsson et al,[51] 2006	Fair	819	7.6	VC	All-cause delivery <37 wk	6.1	-0.94 (-4.09 to 2.22)	0.85 (0.48 to 1.49)
McDonald et al,[52] 1997	Good	480	5.2	OM	All-cause delivery <37 wk	7.6	-0.95 (-5.54 to 3.64)	0.87 (0.46 to 1.67)
McGregor et al,[53] 1994	Good	129	10.9	VC	All-cause delivery <37 wk	7.3	7.75 (-3.16 to 18.66)	2.07 (0.73 to 5.84)
Subtil et al,[55] 2018	Good	2860	1.6	OC	All-cause delivery from 22 to 37 wk	5.9	0.86 (-1.00 to 2.73)	1.15 (0.85 to 1.56)
Random-effects model for all studies: $Q_5 = 3.48$, $P = .63$, $I^2 = 0.0\%$							0.20 (-1.13 to 1.53)	1.02 (0.86 to 1.20)
Spontaneous preterm delivery								
Carey et al,[45] 2000	Good	1919	10.9	OM	Spontaneous delivery <37 wk	9.4	-0.08 (-2.69 to 2.53)	0.99 (0.75 to 1.31)
Kekki et al,[48] 2001	Good	375	0	VC	Spontaneous delivery <37 wk	3.7	1.09 (-3.00 to 5.18)	1.29 (0.49 to 3.40)
Kiss et al,[49] 2004	Fair	351	3.3	VC	Spontaneous delivery <37 wk	5.7	-2.25 (-6.61 to 2.10)	0.60 (0.22 to 1.62)
Lamont et al,[50] 2003	Good	391	7.2	VC	Spontaneous delivery <37 wk	9.8	-5.80 (-10.82 to -0.79)	0.41 (0.18 to 0.92)
Larsson et al,[51] 2006	Fair	785	7.6	VC	Spontaneous delivery <37 wk	3.1	-0.29 (-2.65 to 2.07)	0.91 (0.40 to 2.03)
McDonald et al,[52] 1997	Good	480	5.2	OM	Spontaneous delivery <37 wk[a]	6.3	-1.76 (-5.81 to 2.29)	0.72 (0.34 to 1.54)
Subtil et al,[55] 2018	Good	2860	1.6	OC	Spontaneous delivery from 22 to 37 wk	4.1	0.70 (-0.88 to 2.28)	1.17 (0.81 to 1.69)
Ugwumadu et al,[56] 2003	Good	410	9.3	OC	Spontaneous delivery from 24 to 37 wk	15.3	-9.96 (-15.77 to -4.14)	0.35 (0.18 to 0.67)
Random-effects model for all studies: $Q_7 = 18.37$, $P = .01$, $I^2 = 61.9\%$							-1.44 (-3.31 to 0.43)	0.78 (0.56 to 1.07)

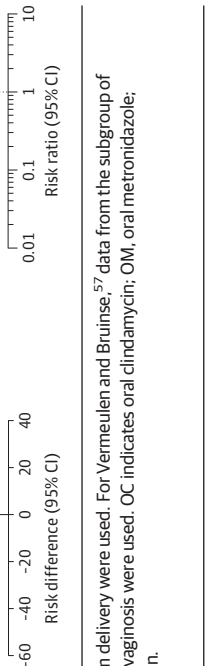


Mixed-methods test of moderators for all-cause vs spontaneous preterm delivery: $P = .054$ for absolute risk difference and $P = .002$ for risk ratio. OM indicates oral metronidazole; PTD, preterm delivery; VC, intravaginal clindamycin.

[a] Includes spontaneous late abortion (≥16 weeks).

Figure 4. Effect of Treatment of Bacterial Vaginosis Among Women With Prior Preterm Delivery

Source	Study quality	No. analyzed	Treatment	Outcome description	Control risk, %	Risk difference (95% CI)	Risk ratio (95% CI)
Preterm delivery <37 wk							
Carey et al[45], 2000	Good	160	OM	All-cause delivery <37 wk (subgroup)	22.5	7.50 (-6.09 to 21.09)	1.33 (0.79 to 2.26)
Hauth et al,[47] 1995	Fair	177	OM	All-cause delivery <37 wk (subgroup)	57.1	-18.30 (-33.90 to -2.70)	0.68 (0.49 to 0.93)
Morales et al,[54] 1994	Fair	80	OM	Spontaneous delivery <37 wk	44.4	-26.26 (-46.10 to -6.43)	0.41 (0.20 to 0.85)
McDonald et al,[52] 1997	Good	34	OM	Spontaneous delivery <37 wk (subgroup)	35.3	-29.41 (-54.73 to -4.09)	0.17 (0.02 to 1.24)
Preterm delivery <34 wk							
Vermeulen and Bruinse,[57] 1999	Fair	22	VC	All-cause delivery <34 wk (subgroup)	9.1	0.00 (-24.03 to 24.03)	1.00 (0.07 to 14.05)
Morales et al,[54] 1994	Fair	80	OM	Spontaneous delivery <34 wk	11.1	-6.57 (-18.54 to 5.40)	0.41 (0.08 to 2.11)



Mixed-methods test of moderators for all-cause vs spontaneous preterm delivery at less than 37 weeks' gestation (P = .14). For Hauth et al,[47] data from the subgroup of participants with bacterial vaginosis and history of prior preterm delivery were used. For Carey et al,[45] data from the subgroup of participants with a history of prior preterm delivery were used. For McDonald et al,[52] data from the subgroup of participants with bacterial vaginosis and history of prior preterm delivery were used. For Vermeulen and Bruinse,[57] data from the subgroup of participants with bacterial vaginosis were used. OC indicates oral clindamycin; OM, oral metronidazole; VC, intravaginal clindamycin.

delivery (Figure 4).[54,57] In Morales et al (n = 80),[54] 4 participants (11%) in the placebo group and 2 participants (4.6%) in the oral metronidazole group had a spontaneous preterm delivery at less than 34 weeks (calculated ARD, −6.57% [95% CI, −18.5% to 5.40%]). Vermeulen and Bruinse[57] reported the incidence of all-cause preterm delivery at less than 34 weeks' gestation among a subgroup of 22 participants with bacterial vaginosis and observed 1 event in both the vaginal clindamycin and the placebo group.

With respect to other pregnancy outcomes, Morales et al (n = 80)[54] reported a significant treatment effect on preterm labor (calculated ARD, −50.51% [95% CI, −69.41% to −31.60%]), premature rupture of membranes (calculated ARD, −28.79% [95% CI, −45.37% to −12.21%]), and birth weight less than 2500 g (calculated ARD, −19.7% [95% CI, −38.13% to −1.26%]). Vermeulen and Bruinse (n = 22)[57] reported no significant treatment effect on neonatal sepsis.

Preterm Delivery Based on Bacterial Vaginosis Clearance Status

Some studies conducted among a general obstetric population reported preterm delivery outcomes for subgroups of participants who had documented clearance or persistence of bacterial vaginosis after treatment. Among a subgroup of participants who had follow-up Gram staining after initial testing and treatment, Carey et al (n = 1704)[45] reported no significant difference in preterm delivery among women with clearance of bacterial vaginosis (incidence, 10.6%) vs those with persistence of bacterial vaginosis (incidence, 10.7%) (P = .95). Kekki et al[48] also reported no significant difference in preterm delivery between active treatment and control among a subgroup (n = 121) of women with documented clearance of bacterial vaginosis 1 week after treatment (calculated ARD, 2.30% [95% CI, −1.45% to 6.06%]).

Harms of Treatment

Key Question 5. What are the harms of treatment of bacterial vaginosis in pregnant adolescents and women?

Fourteen studies reported on the harms of treatment. Eight RCTs reported on maternal adverse events,[45,48,49,51,52,55-57] and 6 studies reported on adverse outcomes in children exposed to medication in utero.[58-63] eTable 6 in the Supplement provides an assessment of individual study methodological quality.

Maternal Adverse Events

Among the 13 RCTs reporting on the benefits of treatment for bacterial vaginosis during pregnancy (KQ4), 8 (n = 7758) reported on maternal adverse events. These 8 RCTs included 4 trials of intravaginal clindamycin,[48,49,51,57] 2 trials of oral clindamycin,[55,56] and 2 trials of oral metronidazole.[45,52] Results from individual studies are presented in eTable 7 in the Supplement. Across this body of evidence, maternal adverse events from treatment with oral clindamycin or oral metronidazole generally occurred at a higher incidence compared with control treatment but were not severe (eg, gastrointestinal symptoms, candida infection). For example, in Carey et al (n = 1704; oral metronidazole),[45] the ARD for gastrointestinal symptoms was 12.5%, and in Subtil et al (n = 2860; oral clindamycin),[55] the ARD was 1.2%. Adverse events from intravaginal clindamycin were infrequent and mild (eg, vaginal itching).

Adverse Childhood Outcomes Associated With In Utero Exposure to Medication

Six studies (eTable 8 in the Supplement) reporting adverse childhood outcomes associated with in utero exposure to metronidazole were included.[58-63] Three observational studies (n = 62 271)[60-62] and 2 meta-analyses[58,59] reported on outcomes related to congenital abnormalities and malformations, and 1 observational study (n = 328 846)[63] reported on incidence of childhood cancer. One study was assessed as poor methodological quality because of confounding and because of a large amount of missing data[61]; however, it was retained for continuity with the previous review. All other studies were assessed as fair methodological quality.

The studies included for this KQ did not provide information about the indication for metronidazole treatment; the setting of treatment (ie, inpatient vs outpatient); or the dose, duration, and route of treatment. Furthermore, the populations were not limited to women exposed to metronidazole specifically for the treatment of bacterial vaginosis in pregnancy, which may limit applicability; however, those studies were retained in this update for continuity with the previous review.

The 2 included meta-analyses found no significant association between metronidazole and congenital malformations (OR, 0.96 [95% CI, 0.75 to 1.22; N not reported][58] and OR, 1.08 [95% CI, 0.90 to 1.29; n = 199 451][59]). Similarly, 2 of the 3 observational studies[60-62] found no association between metronidazole and congenital abnormalities. The exception was reported by Czeizel and Rockenbauer.[60] This fair-quality study (n = 47 963) found a significant association between congenital anomalies and exposure to metronidazole during the first month of gestation (OR, 2.24 [95% CI, 1.30 to 3.85]) but not for the second through third months or fourth through ninth months.[60] The authors noted that because the first month of gestation is counted from the first day of the last menstrual period, several of these weeks of exposure may be before conception or during the all-or-none phase of fetal development; thus, this finding may be spurious or the result of recall bias or uncontrolled confounding.[60]

One cohort study among women enrolled in Tennessee Medicaid did not find an association between metronidazole exposure during pregnancy and diagnosis of first cancer before age 5 years among exposed children (n = 328 846; adjusted RR, 0.81 [95% CI, 0.41 to 1.59]).[63]

Discussion

This evidence report reviewed studies on the diagnostic accuracy of screening tests for bacterial vaginosis and studies evaluating the benefits and harms of metronidazole or clindamycin treatment in pregnancy. **Table 3** summarizes the evidence by KQ and provides an assessment of the strength of evidence. Compared with the 2008 review for the USPSTF on this topic, 2 RCTs were added and 2 RCTs were excluded. Despite this change in the evidence base, the overall conclusions about no benefit in a general obstetric population remain unchanged from the prior report.

For diagnostic accuracy (KQ2), the strength of evidence was assessed as low for adequate accuracy for all tests evaluated because of fair methodological quality and inconsistency. Most studies were conducted among symptomatic, nonpregnant women; thus, the applicability to asymptomatic pregnant women is not clear. For complete Amsel and modified Amsel clinical criteria, the sensitivities observed in the 2 studies[23,40] conducted exclusively among pregnant women were lower than the pooled summary estimates, suggesting that the physiologic changes that occur in the vaginal environment during pregnancy may affect the sensitivity of 1 or more of the clinical criteria used to identify bacterial vaginosis. Furthermore, a lower sensitivity was not observed for the BD Affirm test in the 1 study conducted exclusively in pregnant women.[41] Although no formal comparative assessment was conducted, the tests varied somewhat in accuracy. The laboratory-based tests (BD Affirm VPIII [Becton, Dickinson], BD Max, OSOM BVBLUE [Sekisui Diagnostics]) had higher sensitivities than those based on Amsel clinical criteria but lower specificities.

Among a general obstetric population, the strength of evidence was moderate for no benefit of treatment on all-cause preterm delivery because of imprecision and low for no benefit of treatment on spontaneous preterm delivery because of imprecision and inconsistency. With respect to precision, although most studies were powered for the outcome of preterm delivery, either a lower control group risk was observed than was expected or the treatment effect observed was smaller than expected, resulting in imprecise estimates. Regarding spontaneous preterm delivery, the strength of evidence was also influenced by methodological considerations. The consequences related to preterm delivery generally do not differ for medically indicated deliveries vs spontaneous deliveries, and treatment could result in a medical complication that results in delivery after randomization but before the outcome reporting window that would not be captured. In addition, because an indicated preterm delivery is a competing risk to a spontaneous preterm delivery, use of spontaneous delivery outcomes could introduce informative censoring.

Among women with a prior preterm delivery, the strength of evidence for preterm delivery at less than 37 weeks was insufficient because of inconsistency and imprecision. Furthermore, its applicability is limited to treatment with oral metronidazole. A source for the inconsistency in findings could not be identified. Findings from 3 of the 4 studies were based on subgroup analyses, some of which were post hoc. The 2 studies reporting preterm delivery at less than 34 weeks did not observe any significant differences between groups, but results were very imprecise.

Compared with placebo, the strength of evidence for serious maternal adverse events related to treatment was moderate for no difference for oral metronidazole and both oral and intravaginal clindamycin. Compared with placebo, the strength of evidence for minor adverse events was moderate for no difference for intravaginal clindamycin and was moderate for an increase in minor events for both oral metronidazole and oral clindamycin. These bodies of evidence were rated as moderate because of imprecision due to relatively infrequent events.

The strength of evidence for congenital malformations and incidence of cancer among children exposed to metronidazole in utero was insufficient. This evidence comprises observational studies with no more than fair methodological study quality, and despite large sample sizes, the incidence of these types of events was rare, resulting in imprecise estimates. This evidence applies to metronidazole exposure during pregnancy across a range of medical indications and is not specific to treatment for bacterial vaginosis.

Table 3. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery

No. of studies (No. of participants)	Summary of findings	Consistency/precision	Other limitations	EPC assessment of strength of evidence	Applicability
KQ1: Benefits of screening					
No studies	NA	NA	NA	NA	NA
KQ2: Diagnostic test accuracy					
BD Affirm VPIII 5 Cross-sectional studies[36,37,41,44,67] (2936)	Pooled sensitivity, 0.87 (95% CI, 0.80 to 0.92) Pooled specificity, 0.81 (95% CI, 0.73 to 0.88) Pooled LR+, 4.6 (95% CI, 3.1 to 6.8) Pooled LR−, 0.16 (95% CI, 0.11 to 0.26)	Inconsistent[a]; precise[b]	4 of 5 studies with fair methodological quality (unclear enrollment procedures, unclear masking of test results, spectrum bias)	Low for adequate accuracy	Only 1 study conducted in pregnant women; all studies conducted in symptomatic women
BD Max 1 Cross-sectional study[34,69] (1338)	Sensitivity, 0.93 (95% CI, 0.91 to 0.94) Specificity, 0.92 (95% CI, 0.90 to 0.94) LR+, 10.9 (95% CI, 8.3 to 14.5) LR−, 0.08 (95% CI, 0.06 to 0.10)	Unknown consistency; precise[c]	Excluded participants with intermediate flora from analysis	Low[d] for adequate accuracy	Symptomatic women
OSOM BVBLUE 3 Cross-sectional studies[20,27,30] (864)	Sensitivity range across studies, 0.61 to 0.92 Specificity range across studies, 0.86 to 0.99	Inconsistent[e] (more inconsistent for sensitivity than specificity); precise[f] (more precise for specificity than sensitivity)	All studies with fair methodological quality (unclear enrollment, unclear masking of results, spectrum bias)	Low for adequate accuracy	Symptomatic, nonpregnant women
Complete Amsel criteria 15 Cross-sectional studies[20-24,26-35] (7171)	Based on 14 of the 15 studies: Pooled sensitivity, 0.76 (95% CI, 0.63 to 0.85) Pooled specificity, 0.95 (95% CI, 0.89 to 0.98) Pooled LR+, 14.1 (95% CI, 6.8 to 29.2) Pooled LR−, 0.26 (95% CI, 0.17 to 0.39)	Inconsistent[g]; precise[h] (more precise for specificity than sensitivity)	12 of 15 studies with fair methodological quality (unclear enrollment, unclear masking of test results, spectrum bias), heterogeneity in application of clinical criteria and unit of analysis (patients vs visits)	Low for adequate accuracy	Only 1 study conducted exclusively in pregnant women; most studies conducted in symptomatic women
Modified Amsel criteria 5 Cross-sectional studies[23,33-35,40] (2674)	Based on 4 of the 5 studies: Pooled sensitivity, 0.67 (95% CI, 0.54 to 0.78) Pooled specificity, 0.96 (95% CI, 0.93 to 0.98) Pooled LR+, 17.3 (95% CI, 10.4 to 28.8) Pooled LR−, 0.34 (95% CI, 0.24 to 0.48)	Inconsistent[i] (more inconsistent for sensitivity than specificity); precise[j] (more precise for specificity than sensitivity)	4 of 5 studies with fair methodological quality (unclear enrollment, unclear masking of test results, spectrum bias)	Low for adequate accuracy	2 studies conducted exclusively in asymptomatic, pregnant women

(continued)

Table 3. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery (continued)

No. of studies (No. of participants)	Summary of findings	Consistency/precision	Other limitations	EPC assessment of strength of evidence	Applicability
KQ3: Harms of screening					
No studies	NA	NA	NA	NA	NA
KQ4: Benefits of treatment					
6 RCTs[45,46,51-53,55] (6307)	All-cause preterm delivery <37 wk in general obstetric population: Pooled ARD, 0.20% (95% CI, −1.13% to 1.53%) Pooled RR, 1.02 (95% CI, 0.86 to 1.20)	Consistent; imprecise[k]	All but 1 study of good methodological quality; no reporting bias detected	Moderate for no benefit of treatment	Applies to treatment of asymptomatic patients with oral or vaginal clindamycin or oral metronidazole; history of prior PTD in this population ranged from 0%-10.9%
8 RCTs[45,48-52,55,56] (7571)	Spontaneous preterm delivery <37 wk in general obstetric population: Pooled ARD, −1.44% (95% CI, −3.31% to 0.43%) Pooled RR, 0.78 (95% CI, 0.56 to 1.07)	Inconsistent[l]; imprecise[m]	All but 2 studies of good methodological quality; no reporting bias detected	Low for no benefit of treatment	Same as previous row
3 RCTs[45,51,55] (5564)	Preterm delivery <32 wk in general obstetric population: Pooled ARD, −0.30% (95% CI, −0.97% to 0.38%) Pooled RR, 0.87 (95% CI, 0.54 to 1.42)	Consistent; precise[n]	1 study of fair methodological quality; outcome was spontaneous PTD in 2 studies and all-cause PTD in the other study; no reporting bias detected	High for no benefit of treatment	Same as previous row
5 RCTs[45,46,50,53,55] (5377)	Birth weight <2500 g in general obstetric population: Pooled ARD, 0.39% (95% CI, −1.74% to 2.53%) Pooled RR, 1.03 (95% CI, 0.83 to 1.29)	Consistent; imprecise[o]	All studies of good methodological quality; no reporting bias detected	Moderate for no benefit of treatment	Same as previous row
3 RCTs[45,50,55] (5149)	Birth weight <1500 g in general obstetric population: Pooled ARD, 0.06% (95% CI, −0.99% to 1.12%) Pooled RR, 1.05 (95% CI, 0.50 to 2.18)	Consistent; precise[p]	All studies of good methodological quality; no reporting bias detected	High for no benefit of treatment	Same as previous row
4 RCTs[46,52,53,55] (3568)	Preterm PROM or PROM in general obstetric population: Pooled ARD, 0.10% (95% CI, −1.32% to 1.52%) Pooled RR, 1.11 (95% CI, 0.72 to 1.72)	Consistent; imprecise[q]	All studies of good methodological quality; no reporting bias detected; 1 study reported PROM while others reported preterm PROM	Moderate for no benefit of treatment	Same as previous row

(continued)

Table 3. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery (continued)

No. of studies (No. of participants)	Summary of findings	Consistency/precision	Other limitations	EPC assessment of strength of evidence	Applicability
4 RCTs[45,47,52,54] (451)	Preterm delivery <37 wk (all-cause or spontaneous) in women with prior preterm delivery: ARDs range from −29.4% to 7.5% RRs range from 0.17 to 1.33 Results statistically significant in 3 of the 4 studies favoring treatment	Inconsistent[r]; imprecise[s]	2 studies of fair methodological quality; findings from 3 studies were from subgroup analyses, and it is not clear that they were preplanned Unable to definitively identify source(s) of inconsistency	Insufficient	Applies to treatment of asymptomatic patients with a prior PTD with oral metronidazole
2 RCTs[54,] 123 (102)	Preterm delivery <34 wk in women with prior preterm delivery: ARD 0% in 1 study and −6.57% (95% CI, −18.5% to 5.4%) in other study	Consistent; imprecise[t]	Both studies with fair study quality; results from 1 study were from subgroup analysis	Insufficient	Applies to treatment of asymptomatic patients with a prior PTD with vaginal clindamycin or oral metronidazole
KQ5: Harms of treatment (maternal harms)					
Intravaginal clindamycin 4 RCTs[48,49,51,57] (1718)	Heterogenous outcomes reported No serious AEs observed in 3 studies[49,51,52] Infrequent adverse effects such as candidal vaginitis, troublesome discharge; withdrawals because of itching were infrequent and similar between groups when reported by groups[48,51,57]	Consistent; imprecise[u]	Although RCTs were mostly of good methodological quality, adverse event outcome measurement and reporting were not well described and studies were not powered for adverse events	Moderate for no difference in serious AEs or minor harms (intravaginal clindamycin)	Applies to treatment of asymptomatic pregnant women with bacterial vaginosis
Oral clindamycin 2 RCTs[55,56] (3345)	Serious AEs not observed in either group in 1 study[55]; not reported in the other study[56] Higher incidence of adverse effects with active treatment in 1 study (ARD, 1.79% [95% CI, 0.75% to 2.84%])[55] Higher incidence of stopping medication with active treatment in both studies, but findings were statistically significant in only 1 study (ARD, 3.33% [95% CI, 0.38% to 6.27%][55]; ARD, 3.65% [95% CI, −0.27% to 7.56%][56])	Consistent; imprecise[v]		Moderate for no difference in serious AEs but more minor harms (oral clindamycin and metronidazole)	
Oral metronidazole 2 RCTs[45,52] (2776)	Higher incidence of adverse effects or AEs with active treatment in both studies, but findings were statistically significant in only 1 study (ARD, 12.51% [95% CI, 9.33% to 15.69%][45]; ARD, 2.56% [95% CI, −0.36% to 5.47%][52])	Consistent; imprecise[w]			

(continued)

Table 3. Summary of Evidence for Screening for Bacterial Vaginosis in Pregnant Adolescents and Women to Prevent Preterm Delivery (continued)

No. of studies (No. of participants)	Summary of findings	Consistency/precision	Other limitations	EPC assessment of strength of evidence	Applicability
KQ5: Harms of treatment (harms to children from in utero exposure to medication)					
3 Observational studies[60-62] (62 271) 2 Meta-analyses of observational studies[58,63] (>199 541)	Congenital malformations among children exposed to metronidazole in utero: ORs and RR, estimates from individual studies range from 0.44 to 2.24; CIs range from 0.11 to 4.23 Congenital malformations among children exposed to metronidazole in utero: Pooled OR, 0.96 (95% CI, 0.75 to 1.22)[58] Pooled OR, 1.08 (95% CI, 0.90 to 1.29)[59]	Consistent; imprecise[x]	Studies of poor to fair methodological quality, did not address confounding, variation in outcome definition, potential for recall bias in case-control study Older analyses that did not use current methods for conducting and reporting analyses, included studies were not assessed for risk of bias	Insufficient	Applies to metronidazole exposure across a range of indications (not specific to women with bacterial vaginosis)
1 Observational study[63] (328 846 participants with 1 172 696 person-years)	Cancer incidence before age 5 y among children exposed to metronidazole: adjusted RR, 0.81 (95% CI, 0.41 to 1.59)	Consistency unknown; imprecise[y]	Fair methodologic quality; baseline imbalances between groups and potential for residual confounding	Insufficient	Applies to metronidazole exposure across a range of indications; not specific to women with bacterial vaginosis

Abbreviations: AE, adverse event; ARD, absolute risk difference; EPC, Evidence-based Practice Center; KQ, key question; LR, likelihood ratio; OR, odds ratio; PROM, premature rupture of membranes; PTD, preterm delivery; RCT, randomized clinical trial; RR, relative risk.

[a] The 95% prediction region covers nearly one-third of the receiver operating characteristic (ROC) space (eFigure 1 in the Supplement), suggesting at least moderate inconsistency in estimates across studies not easily be explained by differences in study populations or settings. [b]The 95% confidence region is relatively small and the CI around the area under the curve fairly narrow, suggesting precise estimates (eFigure 1 in the Supplement). [c]Based on the upper and lower CIs for sensitivity and specificity, the LR+ would range from 10.67-11.11 and the LR– from 0.078-0.82, resulting in minimal variation in posttest probabilities, suggesting precise estimates. [d]Overall strength of evidence downgraded for study limitations and a single-study body of evidence with unknown consistency. [e]Range of estimates across the 3 studies inconsistent for sensitivity but reasonably consistent for specificity. In particular, 1 study had markedly lower sensitivity (0.61) than the others (0.88 and 0.917). This study was only reported in ClinicalTrials.gov, and very little information about the study setting and population was available to understand why this result was inconsistent with the other 2 studies. [f]The LR+ and LR– at the upper and lower limits of the sensitivity and specificity CIs for each study are reasonably similar and result in only small differences in posttest probabilities. [g]The 95% prediction region covers more than one-third of the ROC space (eFigure 2 in the Supplement), suggesting at least moderate inconsistency in estimates of sensitivity and specificity not easily be explained by differences in study populations or settings. [h]Confidence region is quite small; thus, estimate was judged as precise, although more precise for specificity than for sensitivity (eFigure 2 in the Supplement). [i]Although the prediction region covers only one-fifth of the summary ROC space, the shape of the region suggests that future studies could lie in the space of relative poor sensitivity and high specificity or equally likely the space of relatively poor specificity and high sensitivity; visual inspection of the plot also suggests inconsistency (eFigure 3 in the Supplement). [j]The 95% confidence region suggests reasonable precision for estimates of specificity but some imprecision in estimates of sensitivity (eFigure 3 in the Supplement). [k]Optimal information size (OIS) criteria not met, sample size of 7116 required to detect a 20% RR reduction based on 9% control group risk, α = .05, power = 0.80, 2-tailed test. Further, the width of the CI around the RR could not exclude a clinically meaningful benefit or harm; despite the narrow range of the CI around the ARD, the population burden from even a small increase or decrease in PTD could be clinically meaningful. [l]Although CIs are mostly overlapping, there is some inconsistency in both the direction and magnitude of effect, as 2 studies observed a statistically significant effect of –5.80% and –9.96%, vs the other studies that are much closer to a null effect (ARDs ranging from –2.25% to 1.09%); I^2 = 61.9% for the ARD. [m]OIS criteria not met; sample size of 9920 required to detect a 20% RR reduction based on 7% control group risk (average risk across studies), α = .05, power = 0.80, 2-tailed test. Further, CIs for both the ARD and RR span a range that could be considered a clinically meaningful benefit or no difference. [n]Low baseline risk (<5%) and sample sizes greater than 2000 in each group; thus, OIS is met. Because of infrequent events, more emphasis was placed on ARD than RR when evaluating precision. [o]OIS criteria not met; sample size of 7116 required to detect a 20% RR reduction based on a 9% control group risk (average across these studies), α = .05, power = 0.8, 2-tailed test. [p]Low baseline risk (<5%) and sample sizes greater than 2000 in each group; thus, OIS is met. Because of infrequent events, more emphasis placed on ARD than RR when evaluating precision. [q]OIS criteria not met; sample size of 24 798 required to detect a 20% RR reduction based on a 3% control group risk (average across these studies), α = .05, power = 0.8, 2-tailed test. [r]Three studies have statistically significant moderate treatment effect sizes; while 1 study shows an increase in preterm delivery from treatment but is not statistically significant (source of inconsistency unexplained). [s]OIS criteria not met; sample size of 1248 required to detect a 20% RR reduction based on 38% control group risk, α = .05, power = 0.80, 2-tailed test. [t]OIS criteria not met; sample size of 1874 required to detect a 20% RR reduction based on 29% control group risk, α = .05, power = 0.80, 2-tailed test. [u]OIS criteria not met; infrequent events reported. [v]OIS criteria not met; sample size of 45 236 required to detect a 20% relative risk increase based on a 2% control group risk, α = .05, power = 0.8, 2-tailed test. [w]OIS study included 155 504 participants[58]; the other study included 199 451 participants[59]; 3 studies overlapped between the 2 analyses. [x]OIS criteria met. Sample size of 17 128 required to detect an elevated RR of 1.20 with α = .05, power = 0.80, 2-sided test. However, the null effect cannot be excluded, and CIs from both the individual studies and the meta-analyses span a clinically meaningful range of benefit and harms; thus, the estimate was considered imprecise. [y]OIS criteria not met; sample size of more than 6 million required to detect a 20% RR increase based on a 0.0142% control group risk, α = .05, power = 0.80, 2-tailed test.

Limitations

This review has several limitations. First, no available evidence that directly evaluated the health benefits and harms of screening (KQ1 and KQ3) was identified. Second, for diagnostic test accuracy (KQ2), limited evidence was available for pregnant, asymptomatic populations. Most studies were of only fair methodological quality, and for most tests, moderate to substantial heterogeneity was observed. Most studies used Gram stain as a reference standard; however, in light of the advances in the molecular and microbiological understanding of bacterial vaginosis, this may be an imperfect standard.

Third, for benefits of treatment (KQ4) and adverse maternal events (KQ5), studies varied with respect to dose and duration of treatment, use of a test of cure, and methodological quality. The findings in women with a prior preterm delivery were inconsistent, and a source for this inconsistency could not be identified. Fourth, with respect to harms, trials were underpowered for maternal adverse events, and the comparative harms of treatment were not assessed.

Fifth, this review was limited to treatment with only metronidazole and clindamycin. Although other treatments for bacterial vaginosis are available, they have not been studied in pregnant women. Sixth, only observational studies were available to assess the harms to children related to in utero exposure to medications (KQ5), and all of these studies included women exposed to metronidazole for any indication, including but not limited to bacterial vaginosis. Given the infeasibility of conducting randomized studies large enough and over a long enough duration to provide definitive evidence on in utero exposure, it is unlikely that this body of evidence will become stronger. However, these medications have had widespread and longstanding use in clinical practice.

Conclusions

Accuracy of screening tests for bacterial vaginosis varies. The evidence suggests no difference in the incidence of preterm delivery and related outcomes from treatment for asymptomatic bacterial vaginosis in a general obstetric population but was inconclusive for women with a prior preterm delivery. Maternal adverse events from treatment appear to be infrequent and minor, but the evidence about harms from in utero exposure was inconclusive.

ARTICLE INFORMATION

Accepted for Publication: January 8, 2020.

Author Contributions: Dr Kahwati had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Administrative, technical, or material support: Kahwati, Clark, Berkman, Patel, Viswanathan.
Supervision: Kahwati, Viswanathan.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under contract HHSA-290-2015-00011-I, Task Order 11, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Heath and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We thank the following individuals for their contributions to this project: AHRQ staff, Tina Fan, MD, MPH, and Tracy Wolff, MD; former AHRQ staff, Quyen Ngo-Metzger, MD, MPH; current and former members of the USPSTF who contributed to topic deliberations; RTI International–University of North Carolina Evidence-based Practice Center staff, B. Lynn Whitener, DrPH; Carol Woodell, BSPH; Sharon Barrell, MA; and Loraine Monroe. USPSTF members, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of the full evidence report underwent external peer review from 4 content experts (Mark Klebanoff, MD, MPH, Nationwide Children's Hospital; John Thorp, MD, University of North Carolina; Valerie J. King, MD, MPH, Oregon Health & Science University; and Julie van Schalkwyk, MD, University of British Columbia) and 2 additional federal partner reviewers (National Institutes of Health; Centers for Disease Control and Prevention). None of the reviewers received compensation for their role in reviewing the report. Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence report.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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