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USPSTF 2020 Recommendations on Screening for Asymptomatic Bacterial Vaginosis in Pregnancy

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EDITORIAL

USPSTF 2020 Recommendations on Screening for Asymptomatic Bacterial Vaginosis in Pregnancy

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Bacterial vaginosis during pregnancy is associated with higher risks of pregnancy complications, including preterm birth, whether or not symptoms are reported. Bacterial vaginosis is currently considered to be a microbial imbalance of the lower genital tract characterized by low levels of "healthy" *Lactobacillus* and overgrowth of a mixed population of other bacterial genera, including *Gardnerella*, *Atopobium*, *Prevotella*, *Mobiluncus*, *Sneathia*, and other taxa. Many of these microbes are also common isolates from sites of intrauterine infection, including the placenta and amniotic fluid. These findings have motivated investigators to conduct clinical trials to examine the potential benefits and harms associated with screening and treatment of asymptomatic bacterial vaginosis in pregnant women, either applied to a general obstetric population or targeting women at increased risk for preterm delivery, such as those with prior preterm birth. This is particularly important in light of growing concerns about the effects of antibiotic use on long-term maternal and child health because of effects on their microbiomes.

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In this issue of *JAMA*, the US Preventive Services Task Force (USPSTF) presents updated recommendations on screening for asymptomatic bacterial vaginosis in pregnancy,[1] along with a supporting evidence review.[2] This issue was last addressed by the USPSTF more than a decade ago.[3] Since then, only 1 additional large clinical study on the topic has been published.[4] Although there are some updates in language, the recommendations remain essentially unchanged.

The new USPSTF report makes 2 recommendations, based on a review of 13 randomized clinical trials (RCTs) evaluating the effect of antibiotic treatment of asymptomatic bacterial vaginosis in pregnancy on the rate of preterm birth. First, the USPSTF "recommends against screening for bacterial vaginosis in pregnant persons not at increased risk for preterm delivery (D recommendation)[1]." Note that the terminology is in transition, with the use of "pregnant persons" intended to include transgender individuals. This recommendation is based on findings from 10 clinical trials that concluded, as a whole, that current treatment strategies for bacterial vaginosis do not reduce the risk of preterm delivery in asymptomatic individuals without prior preterm delivery. Second, the USPSTF also "concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in pregnant persons at increased risk for preterm delivery (I statement)."[1] The updated guidelines do not apply to symptomatic women, who according to guidelines from the US Centers for Disease Control and Prevention should be tested and treated if positive.[5]

The strongest risk factor for preterm delivery is a prior preterm delivery. Of the 13 RCTs evaluated by the task force, 5 reported results for treatment of asymptomatic bacterial vaginosis in pregnant women with prior preterm birth; of these, 4 reported on preterm birth occurring at less than 37 weeks and 2 reported on preterm birth at less than 34 weeks. Three of 4 analyses using the 37-week cutoff presented statistically significant findings in favor of treatment, whereas neither of the 2 analyses using the 34-week cutoff showed significant benefit. Given the limited number of reports and the small sample sizes of these studies, heterogeneity in screening and treatment protocols, and inconsistent results, the USPSTF did not have high confidence in applying these results to clinical care. These recommendations are consistent with current Centers for Disease Control and Prevention guidelines.[5]

The new recommendations noted that the RCTs that were evaluated and the literature in general have shown that maternal harms of screening and treatment for asymptomatic bacterial vaginosis are mostly limited to mild adverse effects of antibiotic use in the mother, such as gastrointestinal upset and vaginal candidiasis, with no fetal harms reported. The USPSTF noted that the use of clindamycin and metronidazole for symptomatic bacterial vaginosis in pregnancy has become the standard of care. Moreover, the USPSTF cited several large studies and meta-analyses of metronidazole treatment in pregnancy (for any indication) that have concluded that the risks of congenital birth defects and cancer are not increased among children exposed to the drug in utero. On the other hand, although not assessed by the USPSTF, there are studies demonstrating that prenatal antibiotic exposure is associated with alterations in the neonatal gut microbiome, which have raised concerns that antibiotic treatment during pregnancy might adversely affect postnatal health.[6]

The new USPSTF Recommendation Statement acknowledges that additional studies are needed to evaluate screening and treatment methods for asymptomatic bacterial vaginosis in pregnancy, particularly for individuals at increased risk for preterm delivery. If further data support a treatment benefit in those at risk for preterm birth, the USPSTF report states that additional efforts should be made to identify those "at risk." Factors acknowledged by the new guidelines

include cervical insufficiency, multifetal gestation, low maternal body mass index, and maternal age (young or advanced), as well as factors involving race/ethnicity (African American, Native Hawaiian/Other Pacific Islander, or American Indian/Alaska Native). Additionally, in a recent meta-analysis, women diagnosed with bacterial vaginosis earlier during pregnancy had higher odds ratios of preterm delivery (2.19 overall, compared with 4.20 and 7.55 at <20 weeks and <16 weeks, respectively).[7] Recent studies that evaluated the molecular fingerprints of vaginal microbiotas concur; samples taken in early to mid-gestation are more sensitive in detecting relationships between microbes and preterm birth compared with samples taken later in pregnancy.[8,9] Some have argued that targeting women in mid-gestation (as late as 28 weeks) for bacterial vaginosis screening and treatment may be too late to counteract the effects of intrauterine infections or inflammation in early pregnancy. A recent meta-analysis concluded that "future studies may need to focus on earlier detection and treatment of bacterial vaginosis in the first trimester of pregnancy, or even preconception."[10]

Strategies directed at prevention of preterm birth through antibiotic treatment of bacterial vaginosis are limited by a poor understanding of what bacterial vaginosis is and how it is mechanistically linked to preterm birth. The gold standard Nugent scoring system, which has been used in many clinical trials for diagnosis of bacterial vaginosis, has significant interobserver variability; in a study including 13 experienced researchers, there was full agreement in diagnosis for only 63% of cases.[11] In an attempt to improve the objectivity and reproducibility of results, and to incorporate findings from detailed studies of the vaginal microbiota, some studies are beginning to link specific bacteria with higher rates of preterm birth, including *Prevotella*,[9,12] *Sneathia*,[8,9] and bacterial vaginosis-associated bacterium 1 (BVAB1),[9] as well as taxonomic subsets of *Gardnerella*,[12] *Ureaplasma,*[13] and others.

Additional molecular diagnostic tests for bacterial vaginosis have also been developed.[14] However, the lack of concordance in the targeted bacteria among these tests highlights the fact that it remains unknown which of the bacteria associated with preterm birth are potentially pathogenic and which are innocuous bystanders, and thus it is not known whether the standard clinical treatments for bacterial vaginosis are targeting the desired bacterial populations. Thus, the observations that have led the USPSTF to conclude that current treatment protocols for asymptomatic bacterial vaginosis in the general obstetric population do not demonstrate clinical benefit do not preclude the possibility that there may be a causal relationship between bacterial vaginosis (or specific microbes associated with bacterial vaginosis) and pregnancy complications.

Other possible reasons for the failure of studies to yield consistent results regarding the effects of treatment of asymptomatic bacterial vaginosis on pregnancy outcomes include imperfect efficacy of (or adherence to) treatment and high rates of recurrence. Most studies did not assess treatment adherence, efficacy, or recurrence of bacterial vaginosis.[15] The most recent PREMEVA trial[4] was intended to address this problem by randomizing study participants with asymptomatic bacterial vaginosis to placebo, 1 course of clindamycin, or 3 successive courses of oral clindamycin, initiated early in pregnancy (mean gestational age at randomization, 12.3-12.4 weeks for all groups). This study reported no significant benefit of either treatment regimen for women with asymptomatic bacterial vaginosis (although very low rates of preterm birth [1.1%] in the population studied was a major limitation of the study). However, as with prior studies, treatment effectiveness and bacterial vaginosis recurrence were not evaluated. Additionally, 20% of women self-reported nonadherence, raising the possibility that an even larger proportion did not take their antibiotics as prescribed. The recurrence risk for bacterial vaginosis is high: 20% to 40% of cases recur within weeks of treatment, and 50% to 70% recur within months.[16,17] Thus, nonadherence, ineffectiveness of treatment protocols, or bacterial vaginosis recurrence could account for the frequently observed lack of effect of treatment on pregnancy outcomes. The most recent Cochrane review on this topic[10] agrees that "subgroups of women in whom bacterial vaginosis was successfully eradicated, and those with recurring bacterial vaginosis, need to be identified and studied more closely in future trials."

Future studies should address how to accurately identify women who may qualify for bacterial vaginosis treatment based on symptoms or (if future studies warrant) risk profiles. Many factors can influence whether a given woman will report symptoms to a particular clinician. The terms "symptomatic" and "asymptomatic" need better definition, especially in pregnancy. Also, whether a woman reports symptoms can be influenced by previous clinical interactions in which she felt ignored or experienced other types of implicit or explicit bias. This might be more common for women of color, as evidenced by findings that how black women communicate key information is often different depending on whether the physician is black or white, suggesting that black women may be more concerned that white physicians may have negative opinions of them.[18] In addition, future studies should consider how to apply risk-based screening in settings where prior medical records may not be available, as recall of prior pregnancy outcomes, including preterm birth, are not always accurate,[19] suggesting that the application of screening guidelines could lead to unintentional bias in the delivery of care. The history of applying screening recommendations for group B *Streptococcus* (GBS) provides a cautionary example of inequalities that can arise in the obstetric setting. Black women are more likely to be carriers of GBS, and their infants are more likely to experience early-onset GBS disease compared with other demographic groups. However, prior to the revised 2002 guidelines recommending universal GBS screening, black women were less likely to be screened for GBS colonization compared with their white counterparts.[20,21] Black women also have higher rates of bacterial vaginosis and preterm birth. Future studies should consider these factors and how they influence the application of screening and treatment for bacterial vaginosis in clinical care settings.

ARTICLE INFORMATION

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