Letters

COMMENT & RESPONSE

Further Considerations Regarding Molecular Screening and Treatment of Bacterial Vaginosis

To the Editor The article by Bretelle and colleagues[1] showed no significant reduction in preterm birth rates by molecular screening and treatment for bacterial vaginosis (BV) among pregnant women who are at low risk of giving birth preterm. Although the authors should be commended, our concerns on the study are as follows.

First, recruiting only low-risk pregnant women might have underestimated the screening effect in light of the objective of the current French study.[1] Among a population of pregnant women, the subpopulation with diabetes is sizable; in Europe, the incidence of gestational diabetes is around 11%, with the highest prevalence being 31.5%.[2] In addition, hyperglycemia in pregnant women is associated with vaginal dysbiosis, and especially the resultant bacterial vaginosis is associated with preterm delivery and premature rupture of membranes.[3] The results of the AuTop trial[1] suggested that molecular screening and treatment for BV can be beneficial to nulliparous women, nearly 50% of the trial participants who are at low risk of preterm birth. However, pregnant women with diabetes, even those who are at risk of preterm birth, seem to make up a sizable population that would be an appropriate target for a BV screening.

Second, the possible existence of iron deficiency in pregnant women might have contributed to the negative results in the current study. A Belgian study[4] recruiting 1900 pregnant women showed that iron deficiency, which was defined as serum ferritin levels less than 15 µg/L, was present in 35% of the population. Another Belgian study[5] reported that subclinical iron deficiency, partly due to inadequate preconceptional iron supply, was associated with vaginosislike microflora during early pregnancy, and serum transferrin receptor concentration greater than 1.45 mg/L was associated with a 3-fold increased risk of vaginosislike microflora. These data might indicate that iron deficiency can predispose pregnant women to bacterial vaginosis, which can potentially cause preterm birth. During the clinical course of antimicrobial treatment of BV, it is supposed that baseline iron deficiency can attenuate the effect of microbials on reducing preterm birth. To prove the possibility, we would like to request the authors to provide additional data on the iron status of the trial participants, if possible, which can help elucidate the extent to which iron deficiency may contribute to the lack of significant between-group difference in preterm birth in the current study. In terms of reducing preterm birth, we believe that iron status screening as part of routine antenatal care should override bacterial vaginosis screening for pregnant women.

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To the Editor The article by Bretelle et al[1] on the effectiveness and costs of molecular screening and treatment for bacterial vaginosis (BV) to prevent preterm birth piqued our interest. The authors conducted a randomized clinical trial among low-risk pregnant women. They found that the screen-and-treat strategy based on Atopobium vaginae (*Fannyhessea vaginitis*) or *Gardnerella vaginalis* quantification did not significantly reduce preterm birth rates. However, they reported a significant benefit with screening and treatment in primiparous women, indicating the possibility of a subgroup effect. This finding suggests that molecular screening and treatment for BV may effectively prevent preterm birth in specific populations.

We applaud the authors' rigorous design, methodology, and use of a novel molecular diagnostic instrument for BV. However, concerns exist regarding the generalizability and clinical relevance of their findings. First, the prevalence of BV in the study population was lower than anticipated (7.3% vs 10%), which may have diminished the intervention's statistical power and prospective impact. Second, the selection of azithromycin as the initial treatment for BV was atypical and needed to be supported by current guidelines, which recommend metronidazole or clindamycin.[2,3] Azithromycin is less effective in vitro against anaerobic bacteria than metronidazole, and it may promote the development of macrolide-resistant strains.[4,5]

Consequently, additional research is required to corroborate the efficacy and safety of molecular screening and treatment for BV during pregnancy, particularly in settings and populations with variable BV prevalence. Noting that BV is a complex disease with multiple etiologies and that various people may have different risk factors and prevalence rates is essential. In addition, it would be beneficial to determine whether alternative treatments, such as metronidazole or clindamycin, are more effective at lowering preterm birth rates.

The efforts of Bretelle et al[1] to advance our understanding of BV screening and treatment during pregnancy are greatly appreciated. However, additional research is required to comprehend this strategy's prospective benefits and limitations.

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Letters

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Further Considerations Regarding Molecular Screening and Treatment of Bacterial Vaginosis

To the Editor Although bacterial vaginosis (BV) is associated with an increase in risk of preterm birth, the US Preventive Services Taskforce's recent evidence review found no studies that directly evaluated the benefit of screening for BV in asymptomatic pregnant persons on reducing preterm delivery.[1] Therefore, the article by Bretelle et al[2] seeks to provide much needed evidence to evaluate the efficacy of screening for BV during pregnancy. Using intention-to-treat analysis, the randomized clinical trial (AuTop) found BV screening before 20 weeks' gestation had no impact on the rate of preterm birth among low-risk pregnant women. However, in post hoc analysis, researchers found the intervention was effective at reducing preterm birth among nulliparous women, but not multiparous women. As this result echoes findings from our own evaluation of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection screening and treatment conducted among pregnant women in Botswana,[3] we were eager to read the potential explanation for the differential finding.

While the rationale for the post hoc analysis stratified by parity was not provided, Bretelle et al[2] hypothesized that the differential impact may be due to nulliparous participants' higher treatment uptake or higher risk for preterm birth. In our *C trachomatis* and *N gonorrhoeae* screening and treatment study, eligibility criteria did not exclude multiparous participants based on preterm risk, and treatment uptake rates were similar between nulliparous and multiparous women; however, we also found that the screening and treatment intervention reduced adverse pregnancy outcomes among nulliparous women after controlling for age, hypertension, and clinic (adjusted risk ratio, 0.33; 95% CI, 0.16-0.69). Similar to Bretelle et al, we found that, among multiparous participants, the intervention had no significant overall effect.

Since age was not a factor in either study, it would be helpful if Bretelle et al provided further discussion of potential mechanisms for the difference in efficacy by parity. For example, in our study, the HIV prevalence was higher among multiparous participants, signaling increased risk of prior exposure to other sexually transmitted infections. Limited research has found that partial protective immunity to *C trachomatis* may develop over time.[4] Therefore, if nulliparous women were less likely to be previously infected, they may experience a more inflammatory upper genital tract infection during pregnancy and screening and treatment would be more effective at decreasing preterm birth. As preterm birth rates remain high globally, and the underlying mechanisms continue to be poorly understood,[5] further research is warranted.

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In Reply We appreciate the interest in our study,[1] which was designed and powered to evaluate the effects of a molecular biology-based point-of-care screening strategy for *Fannyhessea vaginae* and *Gardnerella vaginalis,* followed by treatment in pregnant women at low risk of preterm birth. While the objective of our work was to demonstrate a significant impact on preterm birth on the intention-to-treat study population, which we unfortunately did not, our findings based on post hoc analysis suggested that molecular screening and treatment in nulliparous women can be effective.

In their Letter, Wynn and colleagues report similar findings for effects among nulliparous and multiparous women. They also question whether our study found greater exposure to sexually transmitted infections (STIs) in multiparous women (which might explain the difference between these subgroups). Although we routinely screen patients for STIs and HIV in our practice, these data were not collected in this study. However, this would probably not have influenced our results, given the much lower prevalence of STIs in France than in Botswana (0.1% vs 6.6%, respectively).[2] Nonetheless, we agree with Wynn and colleagues that measuring acquired immunity will be important to more fully understand the results of future trials.

In response to Yanagisawa and colleagues, we strongly agree that diabetes and iron deficiency are risk factors for vaginal dysbiosis. Our study was designed for a low-risk population, as most preterm births occur in women with no obstetrical history. Consequently, women with diabetes were not included in the AuTop trial. On the other hand, although iron concentration is systematically measured at 6 months of pregnancy, we did not collect these data. We agree that these data should be further checked, particularly in the event of treatment failure or recurrence of bacterial vaginosis (BV).

As mentioned by Li and Liu, the prevalence of BV was somewhat lower than expected in our study population and was discussed as a limitation in our article.[1] Li and Liu also questioned the choice of azythromicin as the initial treatment for BV. We agree that the place of azythromicin is not defined in current guidelines for the treatment regimen of BV, but it is not a new treatment. The choice of this treatment was largely based on an earlier preclinical[3] and an in vitro study[4] that showed azithromycin to be more effective than other treatments. Other comparative treatment studies failed to demonstrate the superiority of one treatment over another or to demonstrate the efficacy of conventional treatment of BV.[5,6]

All comments, including our own, suggest that future studies are needed to address these concerns. In this sense, we are implementing a new research program that will evaluate a screening and treatment strategy among this time the high-risk population; our hypothesis being that history of preterm delivery should strongly influence the prevalence of BV and the impact of BV treatment on subsequent pregnancy. Data regarding gestational diabetes, acquired immunity, STIs, and iron deficiency will be collected. In addition, an antibiogram to check for antibiotic resistance will be implemented.

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