Sexual Networks, Sex Hormones, and Recurrent Bacterial Vaginosis: Not Such Strange Bedfellows

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(See the Major Article by Bradshaw et al on pages 777–86.)

Keywords. bacterial vaginosis; sexually transmitted infections; lactobacilli; hormonal contraception; microbiome.

In women of reproductive age, a vaginal environment that is quantitatively dominated by hydrogen peroxide–producing Lactobacillus species typically has a pH considered to be normal (<4.7) and has consistently been associated with healthy pregnancy outcomes, lack of abnormal vaginal symptoms, and reduced risk for acquiring several sexually transmitted pathogens, including human immunodeficiency virus (HIV). The most commonly isolated Lactobacillus species associated with this healthy environment are L. crispatus and L. jensenii. In addition to the direct antimicrobial effects of lactic acid and the consequent acidic pH these bacteria engender, the natural defense mechanisms of the vagina include production of endogenous defenses (including HNP1-3), secretory leukocyte protease inhibitor, cytokines, and endocervical mucous. Bacterial vaginosis (BV) is a very common condition in which these protective lactobacilli are replaced by high quantities of commensal anaerobes, often resulting in symptomatic vaginitis. Relief from antibiotic therapy of BV—metronidazole or clindamycin—is often short-lived, with most women subject to recurrence in the next several months unless ongoing antibiotic therapy (biweekly vaginal metronidazole gel) is used to suppress it [1]. Because BV is associated with adverse health consequences, including elevated risk of HIV acquisition and transmission, preterm delivery [2], and pelvic inflammatory disease [3], and with deleterious effects on sexual and genital health, delineating the pathogenesis of recurrence and optimizing its prevention are major concerns. Critically, the initial event leading to the shift of the anaerobic predominance that characterizes BV is unknown, though data suggest that sex likely contributes—at least in some women.

In this issue of Clinical Infectious Diseases, Bradshaw and colleagues present follow-up on women whose BV was treated with standard week-long oral metronidazole, and who were enrolled in a randomized clinical trial to compare BV cure with the additional therapy of 1 of the following agents: (1) vaginal clindamycin 2% cream, (2) a commercially available cream containing estriol and Lactobacillus acidophilus, or (3) placebo cream. At BV diagnosis, most participants reported abnormal vaginal symptoms. The main study results, which did not demonstrate benefit of either of the additional drugs, have already been published, [4] so this analysis presents a more in-depth evaluation of predictors of remaining free of BV over the period of observation.

In the study reported here, the rate of recurrent BV among those participants who achieved initial cure was measured over 6 months. Retention in prospective follow-up was very good and the rate of recurrent BV very similar to what the few other prospective studies in this area have reported. The study’s key findings include a significantly beneficial effect of use of oral contraceptives containing estrogen during follow-up, and confirmation of these investigators’ earlier finding that having the same sex partner before and after antibiotic treatment for BV was associated with higher rate of BV recurrence than having a new sex partner. Finally, report of male condom use was associated with reduced rates of BV recurrence in this study.

What is most interesting about this paper? Notably, the data build on the important contributions that this Australian group has made in their prospective studies of the vaginal environment in young women, including a very persuasive demonstration that BV is uncommon in...
The absence of any prior sexual contact (including orogenital sex) [5]. In the present study, the investigators cleverly collected not only the “routine” behavioral data used in many clinical trials of sexually transmitted conditions, but went beyond this to characterize the nature of participants’ sexual partnerships by delineating whether their sex partners were consistent or new after, relative to before, treatment for BV. Most of the study participants reported being sexually active with men, and most had a regular male partner at enrollment with whom they maintained sexual contact after treatment. Intriguingly, maintaining the same sex partner—whether male or female—after treatment was associated with a nearly 2-fold increase in likelihood of subsequent BV detection. The investigators made several attempts to account for, and disentangle, the inevitable interactions between condom use and frequency of sexual activity; throughout, the direct association between sex with an established partner remained. While the large and complex nature of most clinical trials preclude collection of more detailed sexual network-level data, asking this simple question about the nature of sex partners yielded a result that was surprising to many investigators—but perhaps not to clinicians who actually care for women with BV—in their first study, and confirmed in this one. These findings nicely align with the little we have learned about how we as humans share our microbiomes—a new paradigm that makes the term “sexually transmitted infection” sound reductive. It is becoming increasingly clear that not only do our individual microbiomes define our internal landscapes, they also likely mediate most of our most intimate encounters with each other—through biofilms, secretions, or just plain skin-to-skin contact. The transmission model that has long been invoked for sexually transmitted infections should be re-examined, and likely reinterpreted, as our study of the human microbiome (genital, oral, and rectal) is integrated into our understanding of disease transmission dynamics.

The other interesting finding of this study relates to participants’ use of a relatively limited selection of contraceptive agents. This allowed the investigators to meaningfully evaluate, in multivariate analysis, the role of estrogen-containing oral contraceptive agents relative to condom use only in supporting a healthy vaginal environment. Hormones have been in the infectious disease news more than usual in the past year, largely with reference to another study indicating a higher risk of HIV acquisition and transmission from women in HIV-serodiscordant partnerships who used hormonal contraception—particularly injectable progesterone—relative to those who did not use it [6]. In the present study, women who used oral contraceptives experienced nearly half the recurrence rate of BV seen in nonusers. While estrogenic support of vaginal epithelium as a source of a healthy Lactobacillus community could explain this observation, other factors could be at play. Without a doubt, the effects of estrogen are complex and include direct effects on intracellular estrogen receptors, which downregulate gene transcription, or indirect interactions with other transcription factors. Estrogen may influence soluble immune mediators in the vaginal environment, as some studies indicating that immunoglobulins, human β-defensins and secretory leukocyte protease inhibitor are lowest at midcycle, when ovulation occurs and estradiol levels are elevated [7–9]. The authors note some of the clinical/epidemiologic evidence supporting an association between hormonal contraception and vaginal microbiology; even more to the point, limited evidence supports that vaginal provision of hormonal contraception might be even more beneficial to the local environment. One study randomized 64 women to either a combined hormonal contraceptive vaginal ring that releases 20 μg/day of ethinyl estradiol (the estrogen component) and 15 μg/day (the active metabolite of desogestrel, a progesterone) or to an oral contraceptive pill containing 20 μg ethinyl estradiol and 100 μg levonorgestrel for 3 consecutive 28-day cycles, followed by crossover to 3 cycles of the drug not initially assigned [10]. Women assigned to contraceptive vaginal ring use had significantly higher quantity of vaginal hydrogen peroxide–positive lactobacilli during follow-up (P < .001).

Some limitations of this analysis highlight areas for future study, and are nicely contextualized in the paper’s excellent discussion. As the investigators note, they could not adequately evaluate a potential differential effect of oral vs injectable contraception, given the low number of women reporting use of the latter. Further exploring the effects of these contraceptive agents—and those of locally delivered products—on the vaginal microbiome is critical, especially with increasing emphasis on “multicomponent prevention” approaches that could integrate local delivery of contraception and antiviral agents to prevent HIV and genital herpes [11]. Equally important, factors that promote the recurrence of BV—or any disrupted vaginal environment not optimally equipped to fend off pathogens or promote sexual and reproductive health—could potentially enhance our care of this frustrating condition, and inform future paths of clinical and pathophysiologic investigation.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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