Vaginal Microbiome and Its Relationship to Behavior, Sexual Health, and Sexually Transmitted Diseases

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Question 1:
There is a known effect on the vaginal microbiota by hormonal contraceptives, as well as a strong negative association between hormonal contraception and bacterial vaginosis. Is there a role for a clinical trial evaluating hormonal contraceptives as part of the treatment for women with recurrent bacterial vaginosis?

Response from Dr. Lewis:
Such a trial would be very interesting, and anything that could potentially improve treatment outcomes for women with recurrent bacterial vaginosis would be most welcome. Careful thought would be needed in the selection of a good control group, however. This is because any form of contraception may affect the vaginal microbiota in ways that are as of yet incompletely understood. For example, there is conflicting evidence about the effect of intrauterine devices (IUDs) on vaginal microflora; this may be due to the fact that researchers have grouped different types of IUDs together in their analyses. Women who do not use or desire to use hormonal contraception might have significantly different behaviors than those who do, which could also affect vaginal microbial communities. Use or nonuse of condoms can also affect the microbiota. Current studies are evaluating the effect of different forms of contraception on the vaginal microbiome, inflammatory markers, transcriptome, and other factors; this information would be extremely helpful in designing a clinical treatment trial for recurrent bacterial vaginosis. For now, a head-to-head clinical trial comparing the effect of estrogen-containing compared with progesterone-only oral contraceptives on the vaginal microbiome might be a good first step in evaluating hormonal contraceptives as treatment, given the association of estrogen with increased glycogen production (and consequently, increased Lactobacillus) in the vagina.
**Question 2:**

What do the authors think is responsible for the inconsistencies in studies on the association between sex practices (oral, anal, and vaginal) and bacterial vaginosis? Are there opportunities for improvements in sample size or study design?

**Response from Dr. Lewis:**

So far, the few studies that compare the association of specific sex practices with bacterial vaginosis have been complicated by several factors. For example, many sexual behaviors are concurrent (e.g., multiple different sex acts and different orders of sex acts can occur in a single sexual encounter) and therefore the influence of one specific sex practice on the vaginal microbiota may be difficult to ascertain. Additionally, the vaginal microbiota is capable of very rapid shifts, so the timing of vaginal sampling as it relates to sex practices may also significantly affect the composition of the microbiome at that time. Some studies of sex practices and the vaginal microbiota have been cross-sectional analyses, which are probably affected by recall bias. Moreover, studies about sexual practices may only ask about sex itself and any effect of other related behaviors, such as lubricant use or hygiene, cannot be ascertained. Currently, there are prospective studies underway that include detailed behavioral diaries and longitudinal vaginal sampling. These studies may allow investigators to more confidently draw conclusions about the effect of specific sexual activity on the composition of the vaginal microbiome.

**Question 3:**

The authors discuss the correlation between cigarette smoking and bacterial vaginosis in epidemiologic studies. Is there any evidence to support a resolution of dysbiosis following smoking cessation?

**Response from Dr. Lewis:**

To my knowledge, this has only been looked at in a fascinating small pilot study by Brotman and colleagues that included both cross-sectional and longitudinal study components. In this study, the vaginal microbiota of smokers was compared with controls who did not smoke; the smokers were significantly more likely to have low Lactobacillus, high diversity microbiota, and high Nugent score. Nine women took part in the longitudinal part of the study, which followed current smokers who were trying to quit. Of the four women who completed the study, all had biomarkers consistent with good compliance with smoking cessation, but only one woman showed potential evidence of a microbial response to smoking cessation. Obviously, a larger study with longer follow-up (>12 weeks) would be useful to confirm or elaborate on these findings.

**Question 4:**

Rwandan sex workers with Lactobacillus crispatus-dominant microbiota had the lowest prevalence of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV). Is there any data, such as an animal model, to support the manipulation of the vaginal microbiome to decrease the risk of STD transmission?

**Response from Dr. Lewis:**

Being able to manipulate the vaginal microbiota in a beneficial manner is a key goal of research, and obviously reproducible, controlled experimental conditions, such as found in a model, are crucial research tools. Several in vitro systems exist, and each has its strengths. One of the most intriguing is a multilayer vaginal epithelial culture system, created by investigators at the University of Texas, that produces glycogen and mucous and is able to support both healthy and dysbiotic microbial communities. Using this model, Pyles et al found that, in HIV-1 infected epithelial cultures colonized with different vaginal microbial communities, viral titers varied significantly in a community-dependent fashion. When the culture model was colonized with single-species Lactobacillus-dominant communities, HIV-1 titers trended lower. This model is still being validated, but so far seems to correspond well to conditions in vivo. As of yet though, no animal model is robust enough to be of good use in exploring preventative or therapeutic strategies involving manipulation of the vaginal microbiota.
Question 5:

Treatment of asymptomatic bacterial vaginosis with intravaginal metronidazole was associated with a decreased incidence of chlamydia in one study, but another study utilizing home screening and treatment did not support those findings. How was home screening implemented in that study, and is there a role for improving the screening and/or treatment of bacterial vaginosis with the goal of decreasing the incidence of other sexually transmitted diseases (STDs)?

Response from Dr. Lewis:

In the large randomized controlled study of home screening (Schwebke et al.), women aged 15–25 years at risk for STDs and with asymptomatic bacterial vaginosis were randomized to a control or a treatment arm. All subjects received a home testing kit by mail every 2 months for 12 months; testing supplies for gonorrhea and chlamydia were also provided at 4, 8, and 12 months after study entry. Subjects self-collected swabs and returned them via U.S. mail. For women in the treatment arm, treatment consisted of oral metronidazole 500 mg twice daily for 7 days at the enrollment visit; when follow-up testing was positive for bacterial vaginosis, women in the treatment arm were notified and treated. All women were treated for gonorrhea or chlamydia infection, if detected. Although the trial included over 1,300 women and was very well designed, there was no significant difference in incident gonorrhea or chlamydia between the arms. This is probably in part due to the inadequate available treatment for bacterial vaginosis. While short-term efficacy of metronidazole is adequate, long-term efficacy is not, and bacterial vaginosis recurs in up to 58% of women within 12 months. It is thought that this may be in large part due to the persistence of biofilm-associated bacteria in the vagina, and current research is beginning to focus on eradication strategies for the multispecies biofilms elaborated by bacterial vaginosis-associated bacteria. If there had been a therapy available during this trial that could reliably eradicate bacterial vaginosis and its biofilms, I suspect we may have seen a decrease in associated STD rates among those who were treated. Additionally, there does seem to be increased risk of incident STD even with intermediate flora, and future studies may show that treatment is indicated for those with Nugent scores of 4–6.

Question 6:

The authors report that bacterial vaginosis has been epidemiologically associated with obesity. Does that correlation persist after adjusting for race and socioeconomic status? It would be interesting to evaluate whether the higher glycemic load and lower nutritional density often found in areas of food deserts have a direct impact on the vaginal microbiome and dysbiosis.

Response from Dr. Lewis:

Obesity has been associated with bacterial vaginosis in large epidemiological studies; one of the largest was one using data from the National Health and Nutrition Examination Survey, 2001–2004. In this study, increasing body mass index (BMI) was associated with bacterial vaginosis in univariate analysis, but the association was not found in the multivariate model. The association of bacterial vaginosis with race, however, did persist. In the United States, the variables of race and socioeconomic status, including educational status, are densely confounded, making the associations between them and disease status difficult to interpret. I agree that the conditions in neighborhoods that may be associated with persons of a particular race or socioeconomic status are likely to have an effect on the microbiome in multiple ways, including through the availability of particular foods. Interestingly, there is some evidence from outside of the United States that supports a direct effect of increasing BMI on the vaginal microbiome. A study performed among 76 Korean women showed that after adjustment for confounding, a Lactobacillus iners-dominant microbiota was significantly associated with obesity in reproductive-age women. Additionally, the proportion of Lactobacillus iners-dominant type increased and Lactobacillus crispatus-dominant microbiota decreased with increasing BMI. The authors
postulate that differences in estrogen, the gut microbiota, or even dyslipidemia could account for this association. Other studies in populations carefully selected to avoid confounding could help further elucidate the relationship between obesity, diet, and vaginal microbial communities.

**Question 7:**

Recently, the American College of Obstetricians and Gynecologists released a Practice Advisory recommending against the practice of vaginal seeding until data is available regarding safety and efficacy (see [http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Vaginal-Seeding](http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Vaginal-Seeding)). Are the authors aware of any emerging evidence regarding the risks and benefits of vaginal seeding, specifically the risk of transmitting asymptomatic maternal infections such as herpes simplex virus or chlamydia trachomatis?

**Response from Dr. Lewis:**

*I am not aware of any new evidence that specifically addresses how vaginal seeding would affect the risk of vertical transmission of asymptomatic maternal infection to the infant. However, unless a cesarean delivery is being performed for cause such as active maternal herpes simplex virus infection, it is hard to postulate that vaginal seeding would expose the infant to more of a potential pathogen or transfer a potential pathogen into more body sites than would vaginal birth. Moreover, if vaginal seeding provides a large benefit to infants, it might be worth a slightly increased risk of vertical transmission of maternal infection, particularly if novel maternal screening protocols could mitigate this risk. However, it is clear that more data are needed on the efficacy of vaginal seeding, particularly since recent evidence from a study of 81 peripartum women and their infants did not demonstrate a significant difference in microbial community structure or function between vaginally versus surgically delivered infants at 6 weeks of age." In this study, the composition and functionality of the microbiota was found to reorganize substantially after delivery and was driven by body site, rather than delivery mode. There is clearly an enormous amount left to learn about determinants of a healthy infant microbiome.*

**References**