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The Vagina Dialogues

Caroline M. Mitchell, MD, MPH and Susan D. Reed, MD, MPH

Department of Obstetrics & Gynecology, University of Washington, Seattle, WA

Only recently, we began to understand that our bodies are not our own – rather, we are hosts to and share space with trillions of microbes that perform valuable, beneficial functions¹. The dialogue between our human cells and these microbial colonizers in part determines health from disease.

The premenopausal human vagina is home to billions of microbes, dominated by species of the *Lactobacillus* genus that make lactic acid and maintain a low vaginal pH. These lactobacilli are supported by the glycogen content of vaginal epithelial cells, driven in part by local estrogen levels – thus we know that menopausal women not using hormone therapy are less likely to be colonized with healthy *Lactobacillus* species than those using hormonal therapy, either local or systemic². It is also known that symptoms of vaginal itching, burning or discomfort affect almost half of postmenopausal women^{3, 4} and can have a significant impact on sexual function and quality of life. However, it is not known whether postmenopausal vaginal symptoms and the vaginal microbiome are connected.

In this issue, Brotman et al describe the composition of the bacterial communities in 30 pre-, 29 peri- and 28 post-menopausal women, and evaluate the relationship between microbes and signs of vulvovaginal atrophy (VVA)⁵. Participants were randomly chosen from women enrolled in a study of human papillomavirus in perimenopausal women. VVA was diagnosed by a standardized clinical exam. The composition of the vaginal microbiota was described using PCR amplification of a conserved portion of the 16S ribosomal subunit gene with subsequent deep sequencing. This methodology captures microbial species not easily cultured - species often associated with vaginal disorders like bacterial vaginosis⁶. Participants were grouped into 5 “community state types” or “CSTs”, defined by the dominant microbe in the community, as previously described by Ravel et al⁷. Not surprisingly, Brotman et al found that most pre-menopausal women had few signs of VVA, and a largely *Lactobacillus*-dominant microbiota. Postmenopausal women were more likely to have VVA and to have a more diverse, non-*Lactobacillus* dominant flora.

The molecular tools used by the authors are powerful and offer new insight into the menopausal microbiome by identifying difficult to cultivate microbial species. However, there are several potential limitations to this analysis. First, as noted by the authors, the forward primer used has multiple mismatches with the common vaginal bacterium *Gardnerella vaginalis*, thus results may not reflect the full complement of vaginal microbes and might misclassify bacterial communities where *G. vaginalis* is actually dominant.

Second, although the authors generated microbial sequences for a novel cohort including peri- and postmenopausal women, they forced their results into the community state type generated by data from premenopausal women, and combined some CSTs for analysis due to low numbers of subjects.

Although vaginitis symptoms in menopausal women have long been attributed to vulvovaginal atrophy, subjective report of symptoms correlates poorly with objective markers of atrophy such as the vaginal maturation index (VMI)⁸. A recent study by Hummelen et al of 32 postmenopausal women showed that vaginal dryness observed by a nurse examiner was associated with decreased abundance of lactobacilli and increased diversity of the vaginal microbiota⁹. However, participant's self-reported vaginal symptoms correlated poorly with the nurse's assessment of atrophy and dryness. Critically, Brotman et al did not report the subjective vaginal complaints of their study participants. Clinically, this is what matters to patients. Few women care what their vaginal microbial "community state type" is as long as their vagina feels normal.

Thus, our challenge. Molecular tools for describing the vaginal microbiome are powerful and certainly enhance our view of the microbial community. However, technology for technology's sake does not further science. Hillier et al demonstrated the lack of lactobacilli and increased diversity in menopausal women using culture-based techniques in 1997¹⁰. Vaginal atrophy seen on exam is associated with low estrogen, which in turn is associated with low levels of colonization with *Lactobacillus* - thus it is not surprising that women with more VVA are less likely to have *Lactobacillus*-dominant flora. The important question is, why do some women have symptoms while others do not? Are symptoms related to atrophy and low estrogen, or to the presence of a microbial colonizer that causes mucosal irritation? Do alterations in the microbiota over time correlate with changes in the vaginal symptom profile? Likely, the answer will not be a simple linear relationship, given the complexity of the vaginal microenvironment and the variety of patient symptoms.

We applaud the attention being paid to the menopausal vagina – however, the small studies to date have focused on biologic signs in isolation, with minimal reference to patient symptoms. Understanding the "vagina dialogues" between microbes and a host's clinical symptoms requires an analysis of all parts to come up with a whole answer to the problem of postmenopausal vaginitis symptoms.

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