The Changing Landscape of the Vaginal Microbiome

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KEYWORDS

- Vaginal microbiome • Pregnancy • Bacterial vaginosis • Preterm birth
- Metagenomics • Microbiota

KEY POINTS

- The vaginal microenvironment is a dynamic ecosystem in which the microbiota play a major role in regulating parameters such as pH and in limiting the growth of potentially harmful organisms.
- Alterations in the vaginal microbiota can impact the community's ability to inhibit pathogenesis of disease-causing organisms in the female urogenital tract.
- Bacterial vaginosis is broadly, but apparently only poorly, defined by the disruption of the normal vaginal ecosystem marked by depletion of lactobacilli and overgrowth of anaerobic bacteria.

INTRODUCTION

The microbiome influences humans in many still underappreciated respects, including, but not limited to, development and growth, immunity, metabolism, and even behavior.[1,2] Most bacterial communities exist in mutualistic relationships with the healthy human host, and it is clear that our microbiota evolved in concert with our genome, the product of which is a true human–microbial symbiosis. However, it is also clear that microbial dysbiosis can result in disease, and the outgrowth of opportunistic pathogens can threaten the health and life of the human host. Fueled in part by the Human Microbiome Project (HMP) of the National Institutes of Health (NIH) and

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similar efforts by other groups worldwide,[3–5] large-scale efforts have been made to define the normal microbiome of healthy individuals across multiple body sites. Facilitated by the advent of next-generation sequencing, a major success of the first phase of these efforts has been the wealth of data generated, which collectively has revealed the previously poorly recognized complexity and dynamic nature of the human microbiome and its stunning impacts on human health and well-being. To further explore the functional role of the microbiome in human health and disease, the NIH has launched HMP2, now termed the *integrative* HMP or iHMP, a second phase of study that mandates a more in-depth "multi-omic" approach to explore host–bacterial interactions and community dynamics in the context of human health and disease.

The Vaginal Microbiome Consortium (vmc.vcu.edu) at Virginia Commonwealth University (VCU) has a two-stage project funded by the NIH HMP1 and iHMP programs. The first stage, the Vaginal Human Microbiome Project, is a cross-sectional community-based study on more than 6000 visitors to multiple women's clinics in Central Virginia, with the goal of investigating the roles of the vaginal microbiome in women's urogenital health. Vaginal and buccal samples were collected from women volunteers older than 18 years, with the exception of women who were incarcerated, independent of their state of health. Embedded within this study is the collection and analysis of samples from approximately 250 monozygotic and dizygotic twin pairs from VCU's Mid-Atlantic Twin Registry.[6] The microbial populations in each sample were defined by high-throughput metagenomic 16S rRNA gene sequencing, whole metagenome shotgun analysis, and by microbiologically culturing, cloning by single colony isolation, and sequencing of the genomes of target bacterial species or taxa. In the Multi-Omic Microbiome Study-Pregnancy Initiative, the second stage of this program, samples from more than 2000 pregnant women and their infants are being collected longitudinally at multiple prenatal visits during their pregnancies, at delivery, and at early postnatal visits. Samples are collected from the vagina, rectum, nares, mouth and skin from each participant older than 15 years who is not incarcerated and who is not a surrogate.

Samples from these participants are subjected to six omics technologies: (1) targeted 16S rRNA gene surveys to generate species-level microbiome profiles; (2) whole genome sequencing of relevant taxa that we are able to culture and bacteriologically clone; (3) whole metagenomic shotgun sequencing to generate "gene-centric" and "taxonomy-centric" profiles of the metabolic and pathogenic potential, and to generate genome sequences of abundant taxa that we are unable to cultivate; (4) metatranscriptomic analysis to assess expression levels of relevant prokaryotic and host genes; (5) metabolomic/lipidomic analyses to provide insight into the signaling and regulatory pathways controlling the environment in the vagina; and (6) immunoproteomic analyses to measure cytokines and immune factors impacting vaginal function during pregnancy. The objective of the latter study is to elucidate the role(s) of the vaginal microbiome in the etiology or prevention of adverse outcomes of pregnancy, with a specific focus on preterm birth (PTB) and stillbirth.

THE VAGINAL MICROBIOME

Microbial communities play fundamental roles in promoting homeostasis in the vagina and in preventing colonization of pathogenic bacteria, but the mechanisms by which they exert their influence are not well defined. Historically, studies of vaginal microbiota applied conventional culture-dependent microbiological strategies, which, because most of the microbial species in these environments are intractable to standard cultivation technologies, produce only a partial picture of the overall microbiome.