

# Cervicovaginal microbiota, women's health, and reproductive outcomes

Samuel J. Kroon, Ph.D.,<sup>a</sup> Jacques Ravel, B.Sc.,<sup>b</sup> and Wilhelmina M. Huston, Ph.D.<sup>a</sup>

<sup>a</sup> School of Life Sciences, University of Technology Sydney, Sydney, New South Wales, Australia; and <sup>b</sup> Institute for Genome Sciences, University of Maryland School of Medicine, Baltimore, Maryland

The human microbiome project has shown a remarkable diversity of microbial ecology within the human body. The vaginal microbiota is unique in that in many women it is most often dominated by *Lactobacillus* species. However, in some women it lacks *Lactobacillus* spp. and is comprised of a wide array of strict and facultative anaerobes, a state that broadly correlates with increased risk for infection, disease, and poor reproductive and obstetric outcomes. Interestingly, the level of protection against infection can also vary by species and strains of *Lactobacillus*, and some species although dominant are not always optimal. This factors into the risk of contracting sexually transmitted infections and possibly influences the occurrence of resultant adverse reproductive outcomes such as tubal factor infertility. The composition and function of the vaginal microbiota appear to play an important role in pregnancy and fertility treatment outcomes and future research in this field will shed further translational mechanistic understanding onto the interplay of the vaginal microbiota with women's health and reproduction. (Fertil Steril® 2018;110:327–36. ©2018 by American Society for Reproductive Medicine.)

**Key Words:** Sexually transmitted diseases, pelvic inflammatory disease, bacterial vaginosis, in vitro fertilization, contraception

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**T**his review addresses recent advances into our understanding of the microbial ecosystem in the human vagina and its role on women's health and reproductive outcomes. We have summarized the most recent knowledge, in the context of prior understanding of how the vaginal microbiota is influenced by menstrual cycle and sex hormones, contraceptives and influences the risk of infections and disease, adverse pregnancy and fertility treatment outcomes.

## LACTOBACILLUS SPP. OFTEN UNIQUELY PREDOMINATE THE HUMAN VAGINAL MICROBIOTA

It is now well accepted that microbes present in or on the human body can

impact immunity, nutrition, and physiology (1–3). The human vagina is unique in that, in healthy states, it is most often characterized by reduced bacterial diversity and the dominance of *Lactobacillus* spp. (~10<sup>7</sup>–10<sup>9</sup> per gram vaginal fluid in reproductive aged healthy women) compared to other microbiota (4). The presence of *Lactobacillus* spp., known to produce copious amount of lactic acid, is directly correlated with vaginal pH <4.5. Lactic acid driven acidity (low pH) has been strongly correlated with protection against cervico-vaginal infections, including HIV and other sexually transmitted infections (5–8).

*Lactobacillus* spp. dominated vaginal microbiota have been intrinsically linked to estrogen production and the accumulation of glycogen in

the upper layers of the stratified vaginal epithelium (9, 10). Beyond lactic acid, *Lactobacillus* spp. beneficial properties are associated with the production of bacteriocins (antimicrobial compounds), adherence to the vaginal epithelia (competitive exclusion of other bacteria), and ability to competitively use available nutrients (11, 12). The physiology of the vaginal *stratum corneum* (SC), consisting of loosely associated cells with glycogen stores, and innate defense mediators (13), is thought to contribute to this site being a niche for *Lactobacillus* spp. However, the exact reason for *Lactobacillus* spp. dominance in the human vagina remains to be fully elucidated. Interestingly, other mammals do not harbor *Lactobacillus* spp. in their vaginal microbiota, and consequentially their vaginal pH is not acidic. However, while the composition of the vaginal microbiota is different, it is hypothesized that it could perform the same functions (14). Factors such as diet and unique environmental exposures have been proposed as potential reasons for these compositional differences (14).

Received June 5, 2018; accepted June 25, 2018.

S.J.K. has nothing to disclose. J.R. has nothing to disclose. W.M.H. has nothing to disclose.

Supported in part by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under awards numbers U19AI084044, R01NR014784, R01NR014826, R01NR014784 and R01AI116799 (to J.R.).

Correspondence: Wilhelmina M. Huston, Ph.D., School of Life Sciences, University of Technology Sydney, P.O. BOX 123, Broadway, Ultimo NSW 2007, Australia (E-mail: [Wilhelmina.Huston@uts.edu.au](mailto:Wilhelmina.Huston@uts.edu.au)).

Fertility and Sterility® Vol. 110, No. 3, August 2018 0015-0282/\$36.00

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<https://doi.org/10.1016/j.fertnstert.2018.06.036>

The development of novel and high-throughput culture-independent methods to characterize the composition and structure of microbiota, supported by advances in next generation sequencing technologies and their reduced cost, have enabled a more in depth characterization of microbiota. In the vaginal microbiota (as discussed further in the next section) these advances have enabled the identification of strong correlations between different states of the vaginal microbiota and risk of infections (15). As a result, an improved understanding of the complexities of the microbial environment of the female reproductive tract is available. Approaches that do not rely on amplifying and sequencing specific taxonomically informative genes (i.e., 16S rRNA gene, *cpn60* [16]), such as metagenomics (sequencing of all genes and genomes in a microbial community) (17) or metatranscriptomics (sequencing all gene transcripts expressed in a microbial community) (18) are contributing to the functional characterization of the microbiota and its interaction with the human host.

## MOLECULAR, CULTURE, AND SEQUENCING CONTRIBUTIONS TO UNDERSTANDING THE ECOLOGY OF THE HUMAN VAGINA

High-throughput 16S rRNA gene sequencing studies examining vaginal bacterial species composition and abundance in reproductive-aged women have shown that there are at least five major types of vaginal microbiota, termed community state types (CST) (19, 20). Four of these CSTs are dominated by either *Lactobacillus crispatus* (CST I), *L. gasseri* (CST II), *L. iners* (CST III), or *L. jensenii* (CST V). Additionally, CST IV does not contain a significant species or quantity of *Lactobacillus* but instead comprised of a polymicrobial mixture of strict and facultative anaerobes including species of the genera *Gardnerella*, *Atopobium*, *Mobiluncus*, *Prevotella*, and other taxa in the order *Clostridiales* (19–21). Further examination of CST IV has revealed distinct clusters within this polymicrobial community type, which have since been denoted subgroups CST IV-A and CST IV-B (20). Subgroup IV-A can contain moderate amounts of *Lactobacillus* spp. (typically *L. iners*) as well as strict anaerobes including *Corynebacterium*, while conversely CST IV-B contains a higher proportion of species associated with bacterial vaginosis (BV). The frequency of these CSTs has been shown to differ in different ethnic backgrounds (19, 22), with CST I more common in Caucasian women and CST IV more common (~40%) in African-American and Hispanic women. The frequency of these CSTs differs not only by ethnicity but also by geographical origins (22–24).

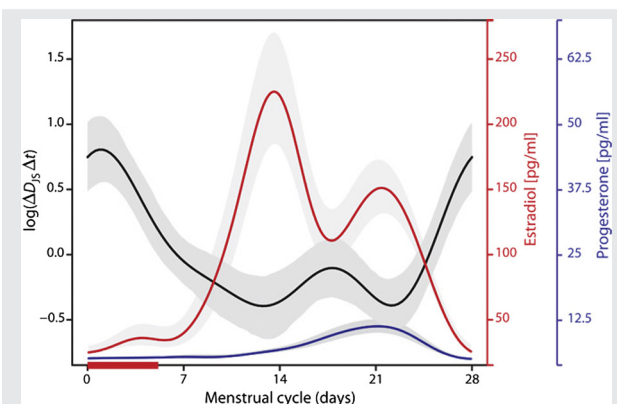
Daily (or frequent) fluctuations in the composition of the vaginal microbiota have been documented by microscopy and cultivation studies (25–27). These findings were confirmed and extended in longitudinal culture-independent analyses performed on vaginal swabs collected twice weekly for 16 weeks (20, 28), or daily for 10 weeks (29) or 4 weeks (4). It was observed that some vaginal microbial communities transitioned in and out of CST IV. The amount of time spent in a particular CST could vary individually as some women experienced consistent and stable CST longitudinal patterns, while others frequently

transitioned between CSTs, most frequently to CST IV (20, 29). In some cases, CST transitions were triggered by menstruation or sexual behaviors, but in other cases they seem to be driven by uncharacterized factors (20). In another longitudinal study, presence of *Gardnerella* was found to be predictive of an impending CST change (30). Phase in the menstrual cycle greatly affects community stability. During ovulation, when estradiol production peaks, stability is highest, while during menstruation, *Lactobacillus* spp. tend to decrease in relative abundance (31), with the exception of *L. iners* (20). In general, molecular and culture-based methods are somewhat in agreement that menses significantly alters the composition of the vaginal microbiota (27,32–34), but change appears to depend on the initial CST present, as well as other factors (20) such as the use of menstrual pads or tampons (20, 35). Figure 1 shows the interplay of microbiome status throughout the menstrual cycle, (20). These longitudinal studies highlight the highly dynamic nature of vaginal microbial communities during the menstrual cycle and emphasize the need to better understand the underlying biological factors modulating fluctuations in composition and functions that affect host physiology. Bayesian network analysis was used to further understanding of the complex interplay between behaviors in menstrual hygiene and microbiota (36). The study highlighted that despite the relatively reduced complexity of the vaginal microbiota, novel approaches integrating more elements of the complex biological system will ultimately improve our understanding of the interactions that drive the vaginal ecosystem and ultimately women's health.

## IMPACT OF HORMONAL CONTRACEPTION ON VAGINAL MICROBIOTA

Because estrogen cycling appears to be linked to vaginal microbiota stability and to some extent composition, several

FIGURE 1



Vaginal microbiota stability and sex hormone levels during the menstrual cycle. The highest stability correlates with high estrogen or progesterone levels, but can be affected by the community state type of the vaginal microbiota, behaviours, and other host factors. Reproduced with permission from AAAS (20).

Kroon. Vaginal microbiota and reproduction. *Fertil Steril* 2018.

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