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Review article

Anaerobes in the microbiome

# The role of the bacterial microbiota on reproductive and pregnancy health

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ABSTRACT

Recent assessments have examined the composition of bacterial communities influencing reproductive, pregnancy and infant health. The Microbiome Project has made great strides in sequencing the microbiome and identifying the vast communities of microorganisms that inhabit our bodies and much work continues to examine the individual contribution of bacteria on health and disease to inform future therapies. This review explores the current literature outlining the contribution of important bacteria on reproductive health among sexually active men and women, outlines gaps in current research to determine causal and interventional relationships, and suggests future research initiatives. Novel treatments options to reduce adverse outcomes must recognize the heterogeneity of the bacteria within the microbiome and adequately assess long-term benefits in reducing disease burden and re-establishing a healthy *Lactobacillus*-dominant state. Recognizing other reservoirs outside of the lower genital track and within sexual partners as well as genetic and individual moderators may be most important for long-term cure and reduction of disease. It will be important to develop useful screening tools and comprehensively examine novel therapeutic options to promote the long-term reduction of high-risk bacteria and the re-establishment of healthy bacterial levels to considerably improve outcomes among pregnant women and sexually active men and women.



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## 1. Introduction

We are just beginning to understand the role, benefit and relation of the microbiome on human health, disease and therapeutic success [1]. The Microbiome Project has made great strides

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in sequencing the microbiome and identifying the vast communities of microorganisms that inhabit our bodies [2] and much work continues to examine the individual contribution of bacteria on health and disease to inform future therapies. Throughout reproductive life, the contribution of microbiota and healthy bacteria, primarily *Lactobacillus* spp., involve the establishment and maintenance of a healthy reproductive tract able to maintain a stable equilibrium and prevent disease. The contribution of microbiota and the balance of these microbes during pregnancy may contribute to the complex process of sustaining the conceptus in-utero and maintaining an adequate gestational period. This review explores the current literature outlining the contribution of microbiota, and important bacteria, on reproductive health among sexually active men and women and the role of microbiota in adverse pregnancy outcomes. Most importantly, this review will critically appraise the current literature regarding the composition of bacterial communities (termed microbiota) and health, discuss the importance of understanding moderators of effects, and outline the need for novel screening programs and new therapies to reduce adverse reproductive, pregnancy and infant outcomes.

## 2. Measurement of microbiota

BV is one of the best-characterized imbalances in the vaginal microbiome. The definition of BV via clinical symptoms (Amsel criteria) or quantification of bacterial morphotypes through Gram stain (Nugent criteria) has advanced with the advent of molecular tools used to identify previously uncultured bacteria and characterize bacterial community structure at the species-specific level [3–5]. BV is now considered a diverse and heterogeneous syndrome associated with different and changing bacterial communities [4–8]. In the molecular era, we have moved beyond Gram staining to characterized the microbiota but Nugent scoring still remains useful given the inexpensive of gram staining, and the ease and reliability of Nugent-BV scores at the low and high ends of the score predicting disease risk.

Pyrosequencing of 16S rDNA genes was recently used to profile the vaginal microbiota of reproductive-age women [3,9]. The microbial communities generally cluster into five community state types (CSTs), four of the community state types (I,II, III and V) are dominated by *Lactobacillus* spp. (*L. crispatus, L. gasseri, L. iners* and *L. jensenii*, respectively) and CST IV-A and IV-B consist of microbial ecosystems with a diverse array of anaerobes including *BV-associated bacterium 1 (BVAB-1), Adopobium vaginae, Dialister, Finegoldia, Peptoniphilus, Megasphaera,* and *Leptotrichia/Sneathia)* and substantially lower numbers of *Lactobacillus* spp [3]. Many of the taxa comprising CST IV have been associated with risk of BV [3]. A more recent report identified two additional major microbial communities, one distinguished on the basis of *G. vaginalis* and the other marked by BVAB1 dominance [9]. At this point, researchers have begun to quantify and measure bacterial contributions to BV disease risk by CST classifications as well as the presence and level of individual BV-associated bacteria. This ecological approach is essential to understand the functional differences and mechanistic basis of risk for BV and other health outcomes to inform and develop individualized treatment options. Among the most pressing issues are to establish better data on the correlations between community structure, Nugent scoring and clinical symptoms.

## 3. Microbiota and reproductive outcomes in sexually-active men and women

The healthy vaginal environment is dominated by *Lactobacillus* species most commonly *L. crispatus* and *L. jensenii* and BV positive women experience a reduction in *Lactobacillus* species and an increase growth of *Adopobium vaginae, Gardnerella vaginalis, Mobiluncus* spp., *Bacteroides* spp., *Provetella* spp., *Eggerthella, Megasphaera, Leptotrichia, Dialister, Bifidobacterium, Slackia* as well as BV-associated bacteria of the Clostridiales Order (BVAB1, BVAB2 and BVAB3) [5,8,10]. Vitali et al. found increased concentrations of *Prevotella, Adopobium vaginae* and *Mycoplasma hominis* distinguished BV positive compared to BV negative women [11] and BV positive women were found to have greater vaginal microbial diversity and decreased *Lactobacilli* spp. stability over time [12–14]. It is important to note, however, that inter-population differences in the distribution of vaginal microbial communities of healthy women complicate the definitions of health and disease states, and may impact the effectiveness of BV treatments [9,14,15]. In asymptomatic, healthy women, *Lactobacillus* dominated communities were found in over 80% of Asian and white women but in only approximately 60% of Black and Hispanic women [14]. Also in the absence of diseases or symptoms, communities with a low level or an absence of *Lactobacillus* species were more commonly found in African American and Hispanic women compared with Asian and white women [14]. As in non-Hispanic white women from the US, the vaginal microbiota of Japanese women is often dominated by multiple *Lactobacillus* species yet within community groups III and IV that are not dominated by *Lactobacillus,* the incidence of intermediate BV was higher for Japanese Black women compared to Japanese White women [16]. A better understanding of the functional consequences of microbiota and bacterial community structure among racial and ethnic subgroups of BV negative, and BV positive, women is urgently needed [17].

Symptomatic BV is a very common condition and rates of BV range from 15% to 30% among sexually active non-pregnant women to over 55% among pregnant women [18,9]. Strong racial disparities in BV are present. African-American and Hispanic women have a higher occurrence of BV than non-Hispanic white and Asian women [19] and ethnicity remains a strong predictor of BV risk independent of other factors including socioeconomic and lifestyle factors [9,20]. Globally, sub-Saharan African women experience the highest reported prevalence of BV with the maximum over 58% in South Africa [21]. Aboriginal and ethnic minority populations are also especially vulnerable. BV diagnosis in non-pregnant ethnic Tibetans living in the Sichuan Provence of China has been reported to be sixty percent and in non-pregnant women from tribal populations in the Fars Province of Iran BV prevalence was 49–50% [21]. Underlying genetic factors that may correlate with ethnicity or geographically defined populations, and gene*environment interactions, could explain some of the health disparity in BV incidence and recurrence[22,23]. Candidate genes that modulate the inflammatory response appear to be important in this regard. In a study of non-pregnant Italian women, for example, women homozygous for either of two genetic polymorphisms in the interleukin-1β (IL-1β) gene were at increased risk of BV [22]. Elsewhere, variants in the corticotropin-releasing hormone receptor gene (CRH-R) have been associated with Nugent scores but among white women the role of the CRH-R and BV differ by smoking status [23]. The same study showed that among black women, variants in the corticotropin releasing hormone gene (CRH) were associated with Nugent scores regardless of smoking status. Moreover, significantly different genotype and allele frequencies of the CRH related risk genes between African-American and white women were reported.

Nugent-defined BV and many BV-associated bacteria have been linked to reproductive sequelae including pelvic inflammatory disease (PID) and increased rates of sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) [24–27]. A recent assessment of stored endometrial and cervical swabs from the PID Evaluation and Clinical Health (PEACH) study evaluated the role of bacteria on endometritis, recurrent PID and infertility. Positivity for