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The global health impact of vaginal dysbiosis

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Abstract

The most common dysbiosis of the vaginal microbiome (defined here as a vaginal microbiome not dominated by lactobacilli) is bacterial vaginosis, an anaerobic polybacterial dysbiosis. Other dysbiotic states of importance to global health are vaginal microbiota with a high abundance of streptococci, staphylococci or *Enterobacteriaceae*, vaginal candidiasis and trichomoniasis. Knowledge about the different types of dysbiosis and their relationship to urogenital and reproductive disease burden has increased in recent years by applying non-culture-based techniques, but is far from complete. The burden of bacterial vaginosis is highest in sub-Saharan Africa and in women of sub-Saharan African descent living elsewhere. Vaginal dysbiosis has been associated with increased susceptibility to and transmission of HIV and other sexually transmitted infections and increased risk of pelvic inflammatory disease, preterm birth and maternal and neonatal infections. In this review, we summarize the contribution of vaginal dysbiosis to the global burden of each of these and highlight areas that require more research.

Keywords: Vaginal dysbiosis; Bacterial vaginosis; HIV; Sexually transmitted infections; Pelvic inflammatory disease; Preterm birth

1. Introduction

We have known for some time that most women have a vaginal microbiome (VMB) that consists predominantly of lactobacilli, and that vaginal dysbiosis (defined here as a VMB that is not dominated by lactobacilli) occasionally causes symptomatic conditions [1]. The most common and best studied clinical condition characterized by vaginal dysbiosis is bacterial vaginosis (BV), which is associated with subclinical vaginal inflammation [1]. Vaginal conditions associated with clinically overt inflammation have also long been recognized: these include desquamative inflammatory vaginitis, atrophic vaginitis, vaginal candidiasis and trichomoniasis [1]. Women with vaginal symptoms, such as unusual vaginal discharge, unusual odor and/or vaginal itching, seeking clinical care, will either receive antibiotic or antifungal treatment empirically, or might be offered diagnostic testing prior to treatment. This diagnostic testing is usually only offered in specialized clinics and is usually limited to microscopic evaluation of vaginal secretions (referred to as a wet mount) and/or vaginal pH determination. In research settings, BV is typically diagnosed by the Amsel criteria, which rely on wet mount microscopy and the presence of clinical criteria [2], or by Gram stain Nugent scoring [3], which relies on microscopy after Gram staining of a vaginal smear (Table 1).

Since the beginning of the new century, molecular laboratory techniques to identify bacteria at the genus and species level have gradually become more available and affordable and are increasingly being employed as a tool in molecular epidemiological studies [4,5]. These molecular studies have now conclusively shown that lactobacilli-dominated VMB are indeed associated with a balanced immune-tolerant vaginal micro-environment and that BV is best described as an anaerobic polybacterial dysbiosis (reviewed in [4]). However,

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Table 1
Description of diagnostic methods for bacterial vaginosis.

Diagnostic method	Clinical and microscopy criteria	Diagnosis
Amsel criteria [2]	1. pH of vaginal secretions >4.5 2. Fishy odor after adding KOH to vaginal secretions 3. ≥20% Clue cells on wet mount 4. White, skim-milk-like vaginal discharge	Bacterial vaginosis: if at least 3 of these 4 criteria are fulfilled
Nugent scoring of Gram-stained vaginal smears [3]	1. Gram-positive rods: score 0–4 ranging from high quantity (0) to none (4) 2. Gram-negative coccobacilli forms: score 0–4 ranging from none (0) to high quantity (4) 3. Curved Gram-negative rods: score 0–2 ranging from none (0) to high quantity (2)	Overall Nugent score – add the 3 scores: 0–3 = Normal microbiome 4–6 = Intermediate microbiome 7–10 = Bacterial vaginosis

these studies have also shown that not all lactobacilli are equal from a clinical point of view: *Lactobacillus crispatus* has consistently been associated with lack of vaginal mucosal inflammation and protection from adverse outcomes, whereas *Lactobacillus iners* is much more easily displaced and often co-occurs with dysbiosis-associated anaerobes, pathobionts and pathogens [4]. The picture is less clear for *Lactobacillus gasseri*, *Lactobacillus jensenii* and *Lactobacillus vaginalis*, but VMB containing a large abundance of those lactobacilli are less common.

Molecular studies are also beginning to shed light on different types of dysbiosis. In a systematic review of 63 molecular studies conducted between 2008 and 2013, all 17 studies that employed hierarchical clustering identified at least one anaerobic polybacterial cluster consistent with BV, and three of the 17 studies also identified clusters that were dominated by, or had high abundance of, a pathobiont (streptococci, staphylococci, or species of the *Enterobacteriaceae* family such as *Escherichia coli*, *Shigella* sp. or *Proteus* sp.) [4]. Some clinicians believe that these VMBs with high abundance of pathobionts are associated with 'aerobic vaginitis' ([6] and discussed by Donders in this journal issue). While the role of vaginal pathobionts (and particularly *Streptococcus agalactiae* and *E. coli*) in invasive maternal and neonatal infections has been well-documented ([7] and discussed by Cools et al. in this journal issue), their potential role in causing a vaginitis syndrome distinct from BV has not yet been universally accepted. However, these vaginal pathobionts are thought to have higher pathogenicity indexes than BV-associated anaerobes, and they might therefore be clinically relevant even when present in relatively low abundance.

2. Current limitations in assessing the global burden of vaginal dysbiosis

Most epidemiological data available to assess the global burden of vaginal dysbiosis and the clinical conditions associated with it are based on Amsel criteria and/or Nugent scoring of vaginal smears (Table 1). Molecular studies have shown that the extent of dysbiosis (no or low abundance of lactobacilli; increased bacterial diversity) correlates well with the Nugent score and with vaginal pH, but not with the other Amsel criteria [4]. We therefore trust that epidemiological studies that have employed Nugent scoring of vaginal smears can still be considered reliable, whereas studies based on Amsel criteria should be interpreted with more caution. However, it is important to keep in mind that Nugent scoring of vaginal smears cannot differentiate between different types of lactobacilli or different types of dysbiosis. Furthermore, our current knowledge about different types of dysbiosis is limited. In recent years, the field has adopted bacterial sequencing as the method of choice to characterize the VMB, but it is likely that additional laboratory methods will have to be employed to enable further clinically relevant dysbiosis differentiation. For example, studies have consistently shown that *Candida* sp. and relatively low-abundant pathobionts co-occur more often with lactobacilli than with BV-associated anaerobes [4,8]. This means that not all women with a *Lactobacillus*-dominated VMB are at low risk of developing adverse outcomes. We hypothesize that women with high abundance of *L. iners* are more likely to harbor *Candida* sp. or relatively low-abundant pathobionts than women with high abundance of *L. crispatus*, but well-powered molecular epidemiological studies are needed to prove this. Furthermore, data from recent vaginal biofilm studies have suggested that BV-associated dysbiosis could be subdivided into dysbiosis with or without biofilm, and that the former could be further subdivided into biofilm including both *Gardnerella vaginalis* and *Atopobium vaginae* (as well as potentially other anaerobes) or biofilm consisting predominantly of *G. vaginalis*, but lacking *A. vaginae* [9]. In addition, some pathobionts might form a vaginal biofilm that is distinct from *G. vaginalis*-containing biofilms [10]. Much more research is needed to improve our understanding of these different types of dysbiosis and their relationships to urogenital and reproductive disease burden.

3. Global burden of symptomatic and asymptomatic vaginal dysbiosis

One of the first population-based studies to estimate BV prevalence using Nugent scoring of vaginal smears was the 2001–2004 National Health and Nutrition Examination Survey in the United States [11]. Among women aged 14–49 years, the BV prevalence (defined as a Nugent score of 7–10) was estimated to be 29.2%, but only 15.7% of the women with a Nugent score of 7–10 reported vaginal symptoms. The BV prevalence was 23.2% among non-Hispanic white women,