



Vaginal Microbiomes Associated With Aerobic Vaginitis and Bacterial Vaginosis

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OPEN ACCESS

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Specialty section:

This article was submitted to Population, Reproductive and Sexual Health, a section of the journal Frontiers in Public Health

Received: 14 July 2017

Accepted: 02 March 2018

Published: 26 March 2018

Citation:

Kaambo E, Africa C, Chambuso R and Passmore J-AS (2018) Vaginal Microbiomes Associated With Aerobic Vaginitis and Bacterial Vaginosis. *Front. Public Health* 6:78. doi: 10.3389/fpubh.2018.00078

A healthy vaginal microbiota is considered to be significant for maintaining vaginal health and preventing infections. However, certain vaginal bacterial commensal species serve an important first line of defense of the body. Any disruption of this microbial barrier might result in a number of urogenital conditions including aerobic vaginitis (AV) and bacterial vaginosis (BV). The health of the vagina is closely associated with inhabitant microbiota. Furthermore, these microbes maintain a low vaginal pH, prevent the acquisition of pathogens, stimulate or moderate the local innate immune system, and further protect against complications during pregnancies. Therefore, this review will focus on vaginal microbial “health” in the lower reproductive tract of women and on the physiological characteristics that determine the well-being of reproductive health. In addition, we explore the distinct versus shared characteristics of BV and AV, which are commonly associated with increased risk for preterm delivery.

Keywords: aerobic vaginitis, bacterial vaginosis, vaginal microbiomes, group B *Streptococcus*, preterm birth

INTRODUCTION

Commensal microbiota associated with the human body influence many aspects of fetal development, physiological function, immunity at mucosal surfaces, susceptibility to diseases and ability to assimilate nutrients (1). As such, commensals in the lower female reproductive tract are significant in maintaining vaginal health as well preventing infections (2).

Human vaginal infections are associated with significantly increased risk of preterm birth in women (3, 4). If untreated, they can lead to pelvic inflammatory diseases (PID), which can cause tubal infertility, ectopic pregnancy, reproductive dysfunction, and adverse pregnancy outcomes (including preterm delivery and low birth weight) (3, 4). Vaginal infections may contribute to the progression of cervical dysplasia, increased risk of post-delivery infections, HIV, and herpes simplex virus-2 (HSV-2) acquisition and transmission (3, 5, 6). However, the unexpected pregnancy outcome and premature birth due to aerobic vaginitis (AV) and bacterial vaginosis (BV) infections in prenatal health services among asymptomatic pregnant women is high in Africa and worldwide (7).

The contribution of AV and BV to vaginal health and pregnancy outcome has been investigated for over a century, yet they remain incompletely understood (8). For example, in epidemiologic studies, it has been suggested that having multiple sexual partners, increased maternal age, previous

spontaneous abortions, and altered vaginal bacterial communities (including decreased *Lactobacillus* species and concurrent colonization with *Candida* species) are the risk factors for vaginal colonization with microbes associated with endogenous infection such as AV and BV (8, 9). However, the unexpected pregnancy outcome and premature birth due to AV and BV infections in prenatal health services among asymptomatic pregnant women are high in Africa and worldwide (7).

THE HEALTHY VAGINAL MICROBIOME

The vagina is a highly nutrient-rich chamber for microbes (10). As a result, the composition of the vaginal microbiota is affected by numerous host factors, including age, changes in hormone levels (during the menstrual cycle, during menopause, pregnancy, or as a result of hormone contraceptive use), other genital infections, as well as sexual and hygiene practices (1, 11). Most of these commensal microbiotas do exist in mutualistic relationships with their human hosts, although a few are opportunistic pathogens that can cause chronic infections, preterm delivery, or life-threatening maternal and fetal diseases (1, 6).

MUTUALISTIC HOST-COMMENSAL RELATIONSHIPS IN THE LOWER FEMALE REPRODUCTIVE TRACT

Several bacterial species colonize both the gastrointestinal and reproductive tracts of women, in addition, the rectum has been suggested to provide an essential source of organisms that commonly colonize the vagina (11). This is of significance since bacteria are repeatedly shed from the body in vaginal secretions, and bacterial regrowth must happen to replenish their number (1).

Some of the required nutrients are derived from host epithelial dead cells, while others are derived from glandular secretions in the lower reproductive tract (1). The vaginal epithelium has a limited blood supply and depends on diffusion of glucose, oxygen, and numerous vital nutrients from underlying submucosal tissues that result in the relatively anaerobic environment at the genital mucosa (12). In addition, the vaginal mucosa undergoes recurring cycles of proliferation of the basal layer, maturation, and desquamation into the vaginal lumen (12).

The vagina harbors a collection of microbes that are distinct from other human surfaces and mucosal sites, with a reduced microbial diversity dominated by *Lactobacillus* species, believed to cause acidification of this environment (13). Furthermore, the ability of lactobacilli to colonize the vaginal mucosa is influenced by the route of delivery and extent of adhesion to vaginal epithelial cells (14).

PHYSIOLOGICAL VAGINAL DISCHARGE AND THE MICROBIOME

Notable changes occur in the physiology, immunology and microbiology of the female reproductive tract following the onset of puberty. The lower reproductive tract before puberty appears

red, due to many blood vessels under the thin hypo-estrogenic mucosa (15). Before puberty, the vaginal pH is close to neutral but not $<0.4.7$, and the microbiome is closely related to the predominant fecal bacterial species.

Healthy women of reproductive age typically have some degree of vaginal discharge, with the quantity and type of secretion varying during the menstrual cycle as a result of hormonal fluctuations (15). Before ovulation, estrogen levels increase, altering cervical mucus from a thicker, sticky consistency to clearer, wetter, more elastic and slippery in preparation for fertilization (16). After ovulation, estrogen levels decline and progesterone levels increase, resulting in cervical mucus becoming thicker, sticky, and less permissive to sperm motility (17).

With the increase of the estrogen levels around puberty, the genital mucosa thickens, becoming a lighter pink in color and becomes colonized with *Lactobacillus* species which produce lactic acid and hydrogen peroxide (H_2O_2) to lower the pH below 4.5 (18). Production of H_2O_2 by certain *Lactobacillus* species is thought to be essential in inhibiting the overgrowth of normal facultative anaerobes (15, 19).

Following puberty, adolescent genital secretions are produced by a number of glands, including the vulva, sebaceous and sweat, appearing white (15). In addition to mucus, other common constituents of these secretions include exfoliated epithelial cells, secretions from the upper reproductive tract, immune molecules, and metabolic by-products (15). This white discharge characteristically does not adhere to the vaginal walls, pools in the posterior fornix, and has an acidic pH of <4.5 (16). In adult women, normal variations in the menstrual cycle, hormonal contraception use, and different stressors may alter the consistency, color, and amount of vaginal discharge (18).

Due to increasing estrogen levels following puberty, sexually matured women have a lower reproductive tract that favors lactobacilli colonization. Estrogen results in thicker stratified epithelia and higher glycogen concentrations with *Lactobacillus* species contributing to a lower pH to ≤ 4.5 in the vagina (10), due to lactic acid and H_2O_2 production. In addition to *Lactobacillus* species, some commensal microorganisms commonly identified in the lower reproductive tract include *Candida albicans*, *Staphylococcus aureus*, and *Streptococcus agalactiae* (group B *Streptococcus*) (20). These can cause changes in discharge if they are not controlled and become overgrown (20).

OTHER COMMON CAUSES OF ABNORMAL VAGINAL DISCHARGE

Abnormal vaginal discharge differs in color and consistency (thin, thick, frothy, yellow, green, gray, or white) compared with physiological (normal) discharge, and frequently is associated with other symptoms, including itching, fishy, and foul smelling (15). Abnormal discharge is typically caused by vaginal infections, although some relatively common non-infectious etiologies occur as well (21).

Infectious causes of abnormal discharge usually include sexually transmitted infections including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma*, and less

commonly HSV-2 and endogenous infections (i.e. dysbiotic outgrowths of common commensal bacterial such as in AV and BV).

Non-infectious causes of vaginal discharge include vaginal douching, using perfumed soaps for cleaning, some laundry detergents, toilet paper, fabric softeners, and other feminine hygiene products that may act as irritants and cause abnormal discharge (22). Sometimes, foreign bodies (such as a retained tampon, condom, or toilet papers) may result in a malodorous or bloody discharge (22).

BACTERIAL VAGINOSIS

Bacterial vaginosis is defined according to the presence of clinical symptoms and increased vaginal pH, typically ≥ 4.5 , existence of white adherent discharge that contains exfoliated epithelial cells with Gram-variable polymorphic rod-shaped bacteria attached to their surfaces (clue cells), and a fishy odor (23). BV is typically polymicrobial, characterized by the presence of mainly anaerobic microorganisms including *Gardnerella vaginalis*, *Prevotella* species, and *Mycoplasma hominis*, *Mobiluncus* species (8, 24, 25). An increased risk of PID, STIs (in addition

to HIV infection), and preterm delivery in pregnant women is associated with BV (13, 26).

AEROBIC VAGINITIS

Aerobic vaginitis was first characterized in 2002 (21), as a vaginal condition distinct from BV, which may require different clinical management and have distinct clinical risks (27). Like BV, AV is defined by disruption in *Lactobacillus* dominance but is accompanied by more extreme inflammatory changes than BV and the presence of mainly aerobic enteric commensals or pathogens, including Group B *Streptococcus* (*S. agalactiae*), *Enterococcus faecalis*, *Escherichia coli*, and *S. aureus* (20, 27–31). AV has been observed in 8–11% of pregnant women (27, 28) and in 5–24% of women reporting vaginal complaints (24, 27).

In certain cases, AV is associated with more genital inflammation, increased numbers of leukocytes visible in vaginal smears, with increased activity to pathogens [termed “toxic leukocytes” (32)]. Women with AV tend to have thinner vaginal mucosa than those with BV, with increased numbers of intermediate and parabasal cells in vaginal smears, indicative of increased turnover and desquamation of superficial epithelial cell layers (32). The comparison of clinical and microbiological characteristics of AV and BV is summarized in **Table 1**.

Both BV and AV diagnosis is based on wet mount microscopy, with diagnosis based on deficiency of *Lactobacillus* species (33). Unlike BV, AV wet mounts are positive for cocci or coarse bacilli, positive for parabasal epithelial cells, and positive for vaginal leukocytes (plus their granular aspect) (30). The diagnosis of AV is also based on molecular diagnostic methods and microscopic criteria graded on a quantitative scale (27, 30) (**Table 2**). Donders et al. (27) have proposed an algorithm for grading AV that is similar to the Nugent scoring system, where the number of points establishes the composite AV score, with the maximum score being 10. Like the Nugent scoring system used for grading BV, the AV score may indicate normal, intermediate, or severe AV (27).

Lactobacillary grades are the basis for a composite score to which the following four variables have been added: (a) proportional number of lactobacilli; (b) the presence of toxic leukocytes; (c) the presence of parabasal epithelial cells; and (d) the type of background microbiota (27).

Aerobic vaginitis, without an accurate diagnosis, might be incorrectly diagnosed as BV, leading to incorrect treatment or even more severe complications of AV such as desquamative inflammatory vaginitis, which is considered to increase the risk

TABLE 1 | Comparison of clinical and microbiological characteristics of aerobic vaginitis (AV) and bacterial vaginosis (BV).

Characteristics	AV	BV
Clinical		
pH	>4.5, usually >6	≥ 4.5
Discharge	Yellowish	White, homogenous
Epithelial inflammation	Present	None
Shed epithelial cells	Parabasal cells	Clue cells
Whiff test (fishy amine odor)	Negative	Positive
Lactobacilli species	Displaced	Displaced
Microbiological		
Common pathogens	Group B <i>Streptococcus</i> <i>Enterococcus faecalis</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i>	<i>Gardnerella vaginalis</i> <i>Atopobium vaginae</i> BVAB2 <i>Megasphaera</i> species
Immunological		
Inflammatory cytokines	High	Moderate
Immune reaction (cytokines)	Reactive	None reactive
Treatment	Kanamycin Clindamycin topical Fluoroquinolones i.e., Ciprofloxacin and ofloxacin	Metronidazole Clindamycin

TABLE 2 | Microscopic diagnosis criteria for aerobic vaginitis (AV) (27).

AV score	# Lactobacillary grades	Number of leukocytes	Proportion of toxic leukocytes	Background flora	Proportion of parabasal epitheliocytes
0	I and IIa	10/hpf ^a	None or sporadic	Unremarkable or cytotoxic	None or <1%
1	IIb	>10/hpf ^a and ≤ 10 /Epithelial cell	50% of Leukocytes	Small coliform bacilli	$\leq 10\%$
2	III	10/Epithelial cell	50% of Leukocytes	Cocci or chains	>10%

^aHigh-power field (hpf) (400x magnification).

Lactobacillary grade I consists of numerous pleomorphic lactobacilli and no other bacteria.

Lactobacillary grade IIa consists of *Lactobacillus* species predominance but with some mixed microbiota: LBG IIb consists also of a mixed microbiota but the proportion of lactobacilli being severely decreased as a result of an increased number of the bacteria.

Lactobacillary grade III consists of lactobacilli severely depressed or absent because of the overgrowth of other bacteria.

of preterm delivery, chorioamnionitis, and funisitis of the fetus during pregnancy (7).

***S. agalactiae* IN AV**

Streptococcus agalactiae (Group B *Streptococcus*) is a member of the commensal microbiota of the human intestinal and genitourinary tracts and is also an important pathogen in AV and other human infections (34). Colonization with GBS is the major risk factor for early-onset invasive GBS disease in newborns (35, 36). GBS rarely cause infections in healthy adults; however, occasionally it may cause morbidity in the elderly, in pregnant women, and in patients with underlying predisposing conditions (34, 35).

Maternal colonization with GBS in pregnant women at delivery is associated with neonatal sepsis, meningitis, and pneumonia (7, 13). The composition of the vaginal microbiota is considered to be very different from that present at other human body sites (13). Currently, GBS is considered to be the leading cause of early-onset sepsis worldwide (37, 38). In addition, GBS and *E. faecalis* are associated with preterm birth, very low birth weight delivery, and puerperal sepsis, which cause substantial morbidity and mortality in sub-Saharan Africa (4, 37, 39).

Prevention of GBS infections in pregnant women and their infants through maternal immunization has been a vision for decades and now is an achievable goal (40). Although GBS can cause asymptomatic bacteriuria, lower urinary tract infection, and acute pyelonephritis, most pregnant women have asymptomatic bacteriuria (40–42). Intrauterine fetal death, chorioamnionitis, and early-onset neonatal disease all are increased among women with untreated GBS bacteriuria (40, 43).

TREATMENT FOR AV AND BV

There is no generally accepted clinical strategy for treating AV (44). AV is treated with antibiotics with intrinsic activity against bacteria of fecal origin, in addition to ensuring minimal interference with vaginal *Lactobacillus* species (44). Antibiotics alone may not be adequate for most patients with AV due to the amount of inflammation typically associated with this condition, including infiltrating leukocytes and parabasal cells (27).

For this reason, the appropriate diagnosis and distinction between AV and BV is very crucial as their treatment is different. Unlike BV, AV does not respond well to metronidazole, which is commonly used for the treatment of *T. vaginalis* and BV (33). Clindamycin is therefore considered to be a better choice than metronidazole for pregnant women with an abnormal vaginal microbiota (45). Fluoroquinolones, such as ciprofloxacin and ofloxacin, have been used in treatment because they have little effect on the normal flora allowing for a rapid recovery from AV (45).

Han et al. (44), proposed that best practice for treating AV would be to base it on microscopy findings with local treatment with any combination of antibiotics (for the infectious agent), topical steroids (to reduce inflammation), and estrogen (to treat atrophy). To accomplish a rapid as well as short-term improvement

for severe symptoms, systemic therapy with moxifloxacin can be used, especially in infections with group B streptococci and for methicillin resistant *S. aureus* (4).

In sub-Saharan Africa countries, sophisticated microbiota detection and administration of clinical interventions are definitely impossible at the moment. Assistance in lowering the morbidity and mortality rate is needed and can only occur if scientists in developing countries use the latest molecular technologies as well genetic investigations to have better understanding of the causes of preterm labor, particularly the triggers produced directly by bacteria or *via* the host, that can lead to irreversible preterm reactions (31). Furthermore, for diagnosis and interventional purpose, products to be applied to the developing world, as well remote and rural areas, must be simple, easy to use, and well understood.

Direct use of probiotics inserted into the vagina is worthy of consideration. However, retention of accessibility of the strains, which are available to the participants in need, appropriate storage, and cost of such capsules, are challenges that will have to be overcome.

CONCLUSION

Maintaining a healthy vaginal environment is considered a challenge worldwide. To prevent the risk of infection, health-care professionals should consider enhancing education to improve women's knowledge of reproductive health and the distinction between AV and BV. We believe that the assessment of healthy vaginal microbiomes, in combination with host genetics, particularly to AV and BV infections and preterm delivery, is urgently needed.

Considering the existing knowledge gap regarding AV, primarily in Africa, there is a need to identify antibiotic sensitivity profiles of the aerobic and anaerobic vaginal pathogens in women of reproductive age to prevent adverse pregnancy outcomes due to opportunistic pathogens, many of which demonstrate antimicrobial resistance (46). The study of vaginal microbiomes will provide an opportunity to define vaginal health, and the link between vaginal infections and commensal opportunistic microbial pathogens in pregnant women. Such surveillance studies will contribute significantly to the literature by establishing epidemiological trends of AV and BV and may well inform about the importance of maternal reproductive health for positive pregnancy outcomes.

AUTHOR CONTRIBUTIONS

Each of the following authors contributed equally to this manuscript: EK, CA, RC, and J-AP.

ACKNOWLEDGMENT

EK received postdoctoral funding from the South African National Research Foundation (NRF) as part of the Department of Science and Technology-NRF CAPRISA Centre of Excellence in HIV Prevention at the University of Cape Town.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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