Ann Ig 2013; 25: 443-456 doi:10.7416/ai.2013.1946

Vaginal microbiota and viral sexually transmitted diseases

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Key words: *Vaginal microbiota, bacterial vaginosis, viral sexually transmitted diseases, lactobacilli*

Parole chiave: *Microbiota vaginale, vaginosi batterica, malattie virali sessualmente trasmesse, lattobacilli*

Abstract

Healthy vaginal microbiota is an important biological barrier to pathogenic microorganisms. When this predominantly Lactobacillus community is disrupted, decreased in abundance and replaced by different anaerobes, bacterial vaginosis (BV) may occur. BV is associated with prevalence and incidence of several sexually transmitted infections. This review provides background on BV, discusses the epidemiologic data to support a role of altered vaginal microbiota for acquisition of sexually transmitted diseases and analyzes mechanisms by which lactobacilli could counteract sexually transmitted viral infections.

Sexually transmitted diseases (STDs) are infections with a significant probability of transmission between humans by means of human sexual behavior and represent a major public health problem, especially in developing countries. STDs have plagued humans for millennia and can result in chronic diseases, pregnancy complications, infertility, and even death. These infections constitute an epidemic of tremendous magnitude, with an estimated 18.9 million persons acquiring a new STD each year. Within this number, 9.1 million (48%) are among young people aged 15-24 (1). These estimates emphasize this age-group's particular vulnerability to STDs. Indeed, STDs are among the first ten causes of unpleasant diseases in young adult males in developing countries and the second major cause of unpleasant diseases in young adult women worldwide. Adolescents and young adults are responsible for only 25% of the sexually active population, yet they represent almost 50% of all newly acquired STDs (1). In addition, reported disease rates underestimate the true burden of infection because the majority of STDs are asymptomatic. It has been suggested that 60% of patients who have one STD will concurrently harbor another sexually transmitted agent (2). Several risk factors are associated with acquisition of STDs, including biological and behavioral factors, cultural influences, lack of information about

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transmission and contraction of STDs, difficulty to access prevention services and number of sexual partners (3).

The accurate identification and effective clinical management of STDs represent clinical strategies for improving reproductive and sexual health, and this is particularly relevant for women, adolescents, and infants, as untreated infections frequently result in severe, long-term complications, including tubal infertility, adverse pregnancy outcomes, cancers, and increased risk of human immunodeficiency virus (HIV) infection (4). In this respect, there is a synergistic relationship between HIV and STDs. Individuals infected with STDs are 2 to 5 times more likely to acquire HIV infection, if exposed to the virus, than healthy subjects. This is related to two factors: 1) ulcerative STDs provide a portal of entry for HIV, and 2) both ulcerative and non-ulcerative STDs create inflammation, which increases the concentration of immune cells in the genital region that serve as targets for HIV (5).

There are more than 30 types of sexually transmitted microbial agents, among which HIV represents the most important. Globally, 34.0 million people were living with HIV at the end of 2011. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV, with 2.5 million new infections and 1.7 million AIDS deaths worldwide (6). According to WHO estimation of curable sexually transmitted infections (7), the most common agents include *Neisseria gonorrheae*, which infects an estimated 106 million people per year worldwide, and is responsible of gonorrhea. This infection is often asymptomatic especially in women and unrecognized female infection during pregnancy can cause neonatal diseases. *Chlamydia trachomatis* causes 105.7 million new infections annually worldwide (7). Genital chlamydial infections are associated with serious complications, in particular pelvic inflammatory disease, tubal factor infertility and ectopic pregnancy in females and epididymitis and reactive arthritis in men (8). Worldwide prevalence of genital human papillomavirus infection is estimated at 440 million persons, causing 510.000 cases of cervical cancer and approximately 288.000 deaths (9). Herpes simplex virus type 2, with 23.6 million new infections/year among 15-49 years old worldwide (10), is the main etiological agent of genital herpes, but may also cause several serious diseases, including keratitis, meningitis and disseminated herpes infection. In addition, the virus may establish latency in the sacral ganglia giving periodical reactivation. *Trichomonas vaginalis* infection is a common sexually transmitted protozoan infection, with an estimated 276.4 million prevalent cases worldwide (7). Serious adverse reproductive health outcomes including pregnancy complications, pelvic inflammatory disease, and an increased risk of HIV acquisition have been linked to *T. vaginalis* infection (11). Syphilis, caused by *Treponema pallidum*, affects an estimated 10.6 million people per year worldwide and between 700.000 and 1.6 million pregnant women, resulting in spontaneous abortions, stillbirths, and congenital syphilis (7, 12).

In Europe, in the mid 90s there has been an increase of bacterial STDs (syphilis, gonorrhea, *Chlamydia trachomatis* infection), especially in large cities and in some population at greater risk (e.g. young homosexuals) (13).

In 2013, Owusu-Edusei and colleagues analyzed STDs costs in the United States. Results indicated that the total lifetime direct medical cost among persons of all ages was $15.6 billion. Total costs were as follows: *Chlamydia trachomatis* costs

$516.7 million, *Neisseria gonorrheae* $162.1 million, hepatitis B virus $50.7 million, HIV $12.6 billion, human papillomavirus $1.7 billion, herpes simplex virus type 2 $540.7 million, syphilis $39.3 million, and trichomoniasis $24.0 million. The analysis evidenced that costs associated with HIV infection accounted for more than 81% of the total cost (14).

Vaginal microbiota and Bacterial Vaginosis

Healthy vaginal microbiota is dominated by *Lactobacillus* spp., but a diverse array of other bacteria can be present in much lower numbers. Over 20 species of *Lactobacillus* have been detected in the vagina, however in the majority of women the healthy vaginal microflora contains one or two *Lactobacillus* species from a range of three or four species, mainly *L. crispatus*, *L. iners*, *L. jensenii* and *L. gasseri* (15, 16). A diverse array of other bacteria such as *Staphylococcus*, *Ureaplasma, Corynebacterium, Streptococcus, Peptostreptococcus, Gardnerella, Prevotella, Clostridium, Bacteroides, Mycoplasma, Enterococcus, Escherichia, Veillonella, Bifidobacterium* and Candida (17-20) can be present but in much lower numbers. Lactobacilli are involved in maintaining the normal vaginal ecosystem by preventing overgrowth of pathogenic and opportunistic microorganisms (21). The principal mechanisms by which lactobacilli exert their protective functions are: (i) competition with other microorganisms for the nutrients and for adherence to the vaginal epithelium, (ii) reduction of the vaginal pH by the production of organic acids, especially lactic acid, (iii) production of antimicrobial substances, such as bacteriocins and hydrogen peroxide (H_2O_2), and (iv) modulation of the local immune system (22).

The microbial communities in the human vagina undergo shifts in the representation and abundance of key species over time that are influenced by factors which may include age, hormonal fluctuations, sexual activity, use of medication and hygiene (20). Therefore, homeostasis of vaginal ecosystem results from complex interactions and synergies among the host and different microorganisms that colonize the vaginal mucosa, and the maintenance of high numbers of resident lactobacilli is an effective hallmark of woman health conditions.

Abnormal vaginal flora involving a strong reduction or disappearance of lactobacilli characterizes two pathologic conditions: bacterial vaginosis (BV) and aerobic vaginitis. Aerobic vaginitis corresponds to a type of disturbed microflora, in which the lactobacilli are replaced by aerobic facultative pathogens from the bowel such as *Escherichia coli*, enterococci, *Staphylococcus* spp. and group B streptococci (23). Bacterial vaginosis (BV) is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing *Lactobacillus* spp. in the vagina with high concentrations of anaerobic bacteria such as *Prevotella* spp., *Mobiluncus* spp., *G. vaginalis*, *Ureaplasma, Mycoplasma*, and other fastidious or uncultivated anaerobes (20, 24). In BV the overgrowing anaerobes produce noxious substances, like polyamines and other compounds that trigger the release of pro-inflammatory cytokines IL-1β and IL-8 (25, 26).

BV represents the most common vaginal syndrome afflicting fertile, premenopausal and pregnant women, with an incidence rate ranging from 20% to 50% (27). Women with BV

typically complain of vaginal discomfort and homogeneous malodorous vaginal discharge, although a substantial fraction of women are asymptomatic (28).

Two methods are used for BV diagnosis: the first was described by Amsel (29) and implies the presence of at least three of the following criteria: (i) thin, homogeneous vaginal discharge; (ii) vaginal pH higher than 4.5; (iii) 'fishy' odor of vaginal fluid after addition of 10% KOH (whiff test); and (iv) presence of clue cells on microscopic evaluation of saline wet preparations. The second method, the Gram stain score of vaginal smears, according to Nugent (30), involves the microscopic quantization of bacterial morphotypes yielding a score between 0 and 10. A Gram stain score ≤ 3 indicates a normal flora, a score of 4-6 represents intermediate flora, whereas a score ≥ 7 is considered indicative of BV.

In recent years, culture-independent techniques based on the analysis of rRNA gene sequences have been developed, providing powerful tools to reveal the phylogenetic diversity of the microorganisms found within the vaginal ecosystem in healthy and pathological conditions. BV is associated with increased taxonomic richness and diversity. The microbiota composition is highly variable among subjects at a fine taxonomic scale (species or genus level), but, at the phylum level, *Actinobacteria* and *Bacteroidetes* are strongly associated with BV. Several vaginal bacteria have been indicated as excellent markers of BV, either alone or in combination, including *Megasphaera*, three novel bacteria in the order *Clostridiales, Leptotrichia/ Sneathia, Atopobium vaginae*, and an *Eggerthella*-like bacterium (15, 31).

There is a large body of evidence that BV, whether is defined clinically, by cultivation, microscopy, or molecular methods and whether it is asymptomatic or symptomatic, is an independent risk factor for severe reproductive tract sequelae, and is associated with pelvic inflammatory disease and tubal factor infertility (32, 33). Changes in the vaginal microbiota have been also associated with obstetrical complications such as late miscarriage and premature birth (34). Therefore the bacterial biota of the human vagina can have a profound impact not only on the health of women but also of their newborns. More importantly, the alterations in the vaginal microbiology have been associated with recurrent urinary tract infections (35) and increased risk to acquire sexually transmitted diseases (36, 37).

Abnormal vaginal flora and Sexually Transmitted Diseases

The cervico-vaginal mucosa represent a portal of entry for different pathogenic microorganisms in women giving infections localized at the genital or systemic level. In healthy women of child-bearing age, the protective mucosa in the vagina is populated with a microflora typically dominated by lactobacilli and their dominance over pathogenic anaerobes is positively associated with vaginal health. Different studies have demonstrated an association between urogenital infections and an altered vaginal microbiota (19, 38-40).

Women with *Lactobacillus* poor flora have an increased susceptibility to sexually transmitted pathogens. Several studies indicate that abnormal vaginal flora lacking lactobacilli is associated with the acquisition of infections by *Neisseria gonorrhoeae, Chlamydia trachomatis,* and *Trichomonas vaginalis* (36, 41-44). Cross sectional and longitudinal studies have demonstrated the association of vaginal microbiota with the prevalence

and incidence of many viral sexually transmitted infections such as human immunodeficiency virus (HIV), human papillomavirus (HPV), herpes simplex virus (HSV) and cytomegalovirus (CMV) infection (36, 40, 45-56, 59, 63-70, 74, 77-79).

HIV

The first clinical studies to suggest an association between abnormal vaginal flora and a viral sexually transmitted infection were reported in mid of 90s on HIV. Initial studies were cross sectional. HIV seropositivity was significantly correlated with BV, independently of other behavioral variables (45-48).

In 1997, Sewankambo and colleagues investigated the association of HIV-1 infection with vaginal flora abnormalities in 4,718 women in Uganda (45). HIV frequency was significantly lower among women with normal vaginal flora (HIV seroprevalence, 14.2%) in comparison to women with severe BV (26.7%). This data were broadly consistent with findings from a smaller investigation of 144 prostitutes in Thailand, in which a positive association between abnormal vaginal flora and HIV-1 seropositivity was found (46). A third study, from Malawi, found that HIV seroprevalence in pregnant women increased from 13% in women with normal vaginal flora to 34% in those with severe BV ($p<0.01$) (47). Lastly, a study from the United States of 724 pregnant women found a trend ($p=0.03$) of increased HIV prevalence with increasingly abnormal flora by Gram stain; 0.8% of women with normal flora to 3.3% with the most abnormal flora (48). These studies demonstrated a positive association between abnormal vaginal flora and HIV-1 seropositivity and a dose-response relationship between the severity of disturbance of the vaginal flora and HIV-1 serostatus.

Longitudinal studies among different populations found associations between BV and HIV-1 acquisition. Data from a prospective survey of 1,196 pregnant women in Malawi found that clinical BV was associated with increased risk of HIV-1 seroconversion during pregnancy and after delivery (49). In 1999, Martin and colleagues enrolled 657 HIV-1–seronegative women, at high risk for sexual acquisition of HIV, into a prospective cohort study to examine the relationship between vaginal colonization with lactobacilli, bacterial vaginosis, and acquisition of HIV (36). During follow-up, at monthly intervals, absence of vaginal lactobacilli on culture was associated with an increased risk of acquiring HIV-1 infection after controlling for other identified risk factors in separate multivariate models. Presence of abnormal vaginal flora on Gram's stain was also associated with increased risk of HIV-1 acquisition. This study demonstrated significant relationships between vaginal colonization with *Lactobacillus* species and risk of acquisition of HIV-1 infection. For HIV-1 infection, a stepwise increase in risk was observed for women with H_2O_2-producing lactobacilli, women with non–H_2O_2-producing organisms, and women lacking vaginal lactobacilli. Thus, for HIV-1 prevention, any lactobacilli appeared to be beneficial, although H_2O_2-producing strains provided the most benefit. Also in other prospective studies the risk of HIV-1 infection increased with increasing severity of the disturbance of vaginal flora, with the highest risk of HIV-1 in women with severe BV (49, 50).

A meta-analysis of individual participant data from 13 prospective cohort studies involving 14,874 women, of whom 791 acquired HIV infection during 21,218 woman years of follow-up has been recently published (51).

Intermediate vaginal flora and bacterial vaginosis were each associated with HIV acquisition in multivariable models when measured at baseline (aHR 1.54 and 1.69, p<0.001) or at the visit before the estimated date of HIV infection (aHR 1.41 and 1.53, p<0.001), respectively, confirming previous observations (52). The risk of HIV acquisition was higher in women with BV than with intermediate vaginal flora.

A systematic review and meta-analysis of the association between bacterial vaginosis and HIV infection indicated that bacterial vaginosis increases the risk of HIV acquisition by approximately 60% (95% CI, 21–113%) (53).

Most cross sectional and longitudinal studies have found that women with BV have higher concentrations of HIV-1 RNA in genital secretions in comparison to women with normal vaginal flora and genital-tract HIV load correlates inversely with *Lactobacillus* species (54-56). Bacteria associated with BV can induce viral replication and shedding in the genital tract (57, 58) which may lead to increased HIV-1 infectiousness for women with BV (59, 60).

The association between BV on female-to-male HIV-1 transmission risk has been recently evaluated in a prospective study of 2,236 HIV-1–seropositive women and their HIV-1 uninfected male partners from seven African countries (61). Participants were followed every three months for up to 24 months. To reduce misclassification, HIV-1 sequence analysis of viruses from seroconverters and their partners was performed to determine linkage of HIV-1 transmissions. HIV-1 incidence in men whose HIV-1–infected female partners had BV was 2.91 versus 0.76 per 100 person-years in men whose female partners had normal vaginal flora (hazard ratio 3.62, 95% CI, 1.74–7.52). After controlling for socio-demographic factors, sexual behavior, male circumcision, sexually transmitted infections, pregnancy, and plasma HIV-1 RNA levels in female partners, BV was associated with a greater than 3-fold increased risk of female-to male HIV-1 transmission (adjusted hazard ratio 3.17, 95% CI, 1.37-7.33).

In conclusion, a *Lactobacillus*-predominant vaginal flora might not only reduce the risk of HIV-1 acquisition in women, but also HIV-1 transmission to male partners, and points to the potential benefits of using the human microbiota to prevent disease.

HSV-2 and CMV

Genital HSV-2 infection is a significant cofactor in the transmission of HIV (62) and, similarly to HIV, this infection is associated with alterations of vaginal flora. In 2003, the first two studies examining the association between HSV-2 and vaginal microbiota were published (63, 64). A study from the United Kingdom on 520 women attending a genitourinary medicine clinic reported that a history of BV was significantly associated with HSV-2 seropositivity (63). In USA 1,207 women were enrolled in a cross-sectional study to identify risk factors for HSV-2 infection (64). Lack of a *Lactobacillus*-predominant vaginal flora was identified as a risk factor for HSV-2 infection. The frequency of HSV-2 infection was lowest among women with normal vaginal flora (14.5%) and was significantly higher among women with BV (41.8%). Similarly, HSV-2 seroprevalence was lowest among women with vaginal *Lactobacillus* that produced hydrogen peroxide (17.8%), intermediate among women colonized by *Lactobacillus* that did not produce hydrogen peroxide (33.7%), and highest among women with no vaginal *Lactobacillus* (38.5%). In multivariable logistic regression analysis, altered vaginal flora remained

an independent predictor of HSV-2 seropositivity. Findings from recent studies on female sex workers also indicated an association between HSV-2 and BV (65, 66).

The association between 5 viral STIs, human papillomavirus (HPV), HIV, herpes simplex viruses types 1 and 2, and Hepatitis C (HCV), and BV among 2,326 women in the general US population has been examined (67). In bivariate analyses BV was strongly associated with all 5 viral STIs. The relationship for HPV (HPV 6, HPV 11) and HCV increased with Nugent category, whereas for HIV, HSV-1, and HSV-2 the prevalence was similar for those in the intermediate and negative categories and highest among those positive for BV. After adjustment for important confounders, only HSV-1 and HSV-2 were significantly associated with the presence of BV. The risk of concurrent HSV-2 infection was 32% higher among women with BV than among women without BV.

BV-associated microorganisms have also been found to be associated with a 2-fold increased risk for incident HSV-2 infection (hazard ratio, 2.1; 95% CI, 1.0–4.5) (68). A longitudinal cohort study on 670 sexually active women was conducted to determine whether the presence of BV is among the risk factors associated with increased rates of HSV-2 acquisition. The study demonstrated that the presence of BV 4 months before the acquisition of antibodies to HSV-2 was an independent predictor of HSV-2 infection.

The association between BV and HSV-2 was confirmed by a study showing that women with prevalent or incident BV had a higher rate of incident HSV-2 than those without this condition (adjusted HR, 2.4; 95% CI, 1.1–5.6). (69). A prospective study on the association between prevalent HSV-2 infection and BV demonstrated that increased prevalence of HSV-2 infection and increased prevalence of BV were each associated with the other (70). The authors concluded that the direction of causality could not be determined since demonstration of causality will require clinical trials that suppress HSV-2 infection, BV, or both. Therefore the relationship between BV and HSV-2 infection can be bidirectional as also suggested by other studies (65, 71).

Bacterial vaginosis is responsible for an increased frequency of reactivation of HSV-2 in the female genital tract. Indeed, in a longitudinal cohort investigation on 330 HSV-2–seropositive women, BV resulted an independent predictor of genital tract shedding of HSV-2 (aOR, 2.3; 95% CI, 1.3–4.0) (72).

Cytomegalovirus (CMV), an important opportunistic pathogen in immune-compromised individuals, is a frequent cause of congenital infection, associated with severe teratogenic complications. In 1991, 175 mothers of neonates with congenital CMV infection were recruited to investigate maternal risk factors for intrauterine transmission of CMV. Data obtained showed that women with BV had a more than 2-fold increased risk of intrauterine transmission of CMV, than women without BV (73). In another more recent study performed to characterize the association between genital tract CMV infection and BV, vaginal wash specimens from 52 women attending an STD clinic were analyzed (74). In this study, BV women not only had increased rates of CMV seroprevalence and CMV seroconversion, but also significantly more women with BV were shedding CMV in lower genital tracts (52%), than those without BV (19%) (OR, 4.5; 95% CI, 1.1-19). In addition, these results suggested that local CMV replication and infection with multiple CMV strains was facilitated by the presence of BV-related microorganisms.

HPV

Genital human papillomaviruses (HPVs) are the central etiological agents in the development of cervical cancer. A first, indirect study on the association of BV with HPV infection was performed in 1994 (75). In this investigation, all cervical intraepithelial neoplasia (CIN) cases analyzed were significantly more common in women with BV, than in women without BV ($p < 0.001$). Therefore, this data suggested the possibility exists that BV is in some way associated with the development of CIN, i.e. as a cofactor to HPV. In a following study, 19 women with cervical HPV infection, in the absence of CIN at enrollment, were examined on average at 7.3-month intervals over a 2-year period (76). At each follow-up visit, cytological and colposcopic examinations were done and vaginal microorganisms were assessed quantitatively by Gram staining of secretions, and anaerobic and aerobic culture. Detection of HPV was significantly associated with isolation of *Gardnerella vaginalis* ($P = 0.03$), *Ureaplasma urealyticum* ($P = 0.04$), *Candida albicans* ($P = 0.01$), *Bacteroides* species ($P = 0.01$), and overgrowth by anaerobes ($P = 0.004$). Normal vaginal flora, characterized by the predominance of *Lactobacillus* species, was, instead, significantly associated with a negative HPV test ($P < 0.001$).

In 2005, Watts and colleagues studied the possible association of BV with HPV infection in 2,256 women (77). Data showed that abnormal vaginal flora was significantly associated with incident and prevalent HPV, but not with duration of HPV infection or development of squamous intraepithelial lesions. In particular, on multivariate analysis the prevalence of HPV infection was significantly associated with intermediate vaginal flora (OR, 1.13; 95% CI, 1.03-1.24) and BV (OR, 1.17; 95% CI, 1.08-1.27). Incident HPV was associated with intermediate score by Gram stain (OR, 1.23; 95% CI, 1.07-1.41) and BV (OR, 1.41; 95% CI, 1.25-1.59). In a cross-sectional study, cervical and vaginal samples were examined to evaluate the association of the vaginal microbiota with HPV infection in 208 Spanish female sex workers (78). Data obtained showed that BV was significantly associated with HPV, in particular with HPV-16-related types, the high risk HPV strains involved in cervical cancer.

In 2011, Gillet and colleagues performed a meta-analysis, in which twelve eligible studies were selected to review the association between BV and HPV infection, including a total of 6,372 women (79). In this work, the overall estimated odds ratio showed a positive association between BV and cervical HPV infection (OR, 1.43; 95% CI, 1.11-1.84). However, the magnitude of association between BV and HPV infection has varied in epidemiological studies and still remains controversial, yielding conflicting results and ranging from absence of any association (80) to a clear positive relationship (79).

Mechanisms of protection by healthy vaginal microbiota against viral STDs

The protection exerted by healthy vaginal microbiota towards viral infections can be ascribed to a direct virucidal effect or to the maintenance of natural defense factors present in the vaginal milieu. Some mechanisms have been suggested by results obtained from in vitro experiments whereas others come from clinical observations in infected women.

Lactobacillus metabolites with known antimicrobial activity may be directly protective for viral infections.

Hydrogen peroxide (H_2O_2) produced by lactobacilli plays an important role as a natural microbicide within the vaginal ecosystem and is toxic to a number of organisms, including HIV-1 (81) and HSV-2 (82). Lactic acid, a final product of carbohydrate metabolism, is produced by all *Lactobacillus* species, and is responsible for physiological acid vaginal pH value (≤ 4.5). Acid pH inactivates HIV (83) and HSV-2 (84). Moreover, HSV-2 is irreversibly inactivated by concentrations of lactic acid giving pH values corresponding to that observed in the healthy human vagina (82).

Several compounds released from lactobacilli can impair the efficiency of target cells in supporting viral replication. A non-protein cell wall component extracted from a vaginal strain of *Lactobacillus brevis* strongly reduced HSV-2 replication in cell culture (85) whereas acid *Lactobacillus* metabolic products decrease activation of T lymphocytes, which may result in decreased lymphocyte susceptibility to HIV-1 infection (86).

A healthy vaginal microbiota contributes to the maintenance of the natural defense mechanisms from invading pathogens. The gel layer that coats the vaginal and cervical epithelium protects women from the acquisition of viral infections. In vitro, cervical mucus has demonstrated the ability to trap HSV in its viscous gel (87). Many of the microorganisms associated with BV are known to produce higher levels of mucinase, sialidase, and other mucin degrading enzymes, compared with the lactobacilli-dominated normal vaginal flora (88-90). Therefore, it is possible that increased degradation of components of the protective mucus layer in women with BV may facilitate binding of HSV-2 and other viruses to the underlying epithelial cell receptors.

It has been suggested that the vaginal proinflammatory cytokines induced by BV-related microorganisms may increase the susceptibility to HIV (91, 92). Indeed, vaginal IL-1β and IL-8 resulted associated with higher cervicovaginal HIV-1 RNA concentrations, even after controlling for plasma viral load (93). Administration of probiotic lactobacilli vaginal tablets produced a significant reduction in IL-1β and IL-6 vaginal cytokines demonstrating the capacity of lactobacilli to modulate the production of inflammatory cytokines in women (94).

Studies have demonstrated that vaginal lactobacilli were able to inhibit the first steps of HSV-2 infection in cell culture (82, 85). The antiviral activity exerted by the presence of lactobacilli during HSV-2 binding to the cell membrane was strain-dependent and appeared directly related to the adhesion capacity of *Lactobacillus* strains (95).

In conclusion, several mechanisms may be involved in the antiviral effect of vaginal lactobacilli: interference with virus attachment or entry into cells, production of metabolites with a direct antiviral effect, production of compounds able to inhibit intracellular events of virus replication and contribution to the maintenance of natural defense factors present in the vaginal milieu.

Conclusion

Healthy vaginal microbiota is important for maintaining vaginal health and preventing infections. Vaginal microbiota consistent with BV or intermediate flora is significantly associated with increased risk for several viral STDs acquisition. Therefore consideration and future research should focus on whether intervention should be recommended to women with an altered microbiota.

Understanding the mechanisms involved in the protection exerted by the physiological microbiota of the vagina will represent an attractive tool to protect against infections.

The results of the studies reported here indicate that a healthy vaginal flora not only protects a woman from the acquisition of sexually transmitted viruses, but also exert a beneficial effect on her partner and sibling by reducing the risk of virus transmission.

Riassunto

Microbiota vaginale e malattie virali sessualmente trasmesse

Il microbiota vaginale, costituito essenzialmente da lattobacilli, rappresenta un'importante barriera biologica contro i microrganismi patogeni. Quando i lattobacilli vaginali sono assenti o in quantità ridotta e sostituiti da una flora anaerobica, una condizione nota come vaginosi batterica, la donna presenta un elevato rischio di sviluppare malattie sessualmente trasmesse. Numerosi studi hanno dimostrato che la vaginosi batterica è associata ad un'aumentata prevalenza e incidenza di infezioni virali a trasmissione sessuale. Questa review fornisce un quadro generale sulle malattie sessualmente trasmesse associate a vaginosi batterica e analizza i possibili meccanismi attraverso cui i lattobacilli possono contrastare la trasmissione di infezioni sessualmente trasmesse.

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