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The vaginal microbiota

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Abstract

The vagina is an ecosystem consisting of various species of microorganisms (microbiota) that play important role in maintaining vaginal health. The vaginal ecosystem includes a variety of species classified into aerobic and anaerobic microorganisms which are vaginal microbiota (VMB). In the vagina of a healthy woman, 70% of normal microbiota is dominated by the *Lactobacillus* species. *Lactobacillus* is a Gram-positive, anaerobic bacterium, and belongs to the group of lactic acid bacteria (LAB). LAB produces lactic acid which plays a role in maintaining vaginal acidity at pH <4, producing H₂O₂ and bacteriocin, modulating non-specific immune responses, and preventing colonization of microorganisms through competitive adhesion in the vaginal epithelium. The composition of the VMB can vary between women and can change dramatically in a short time in the same individual. Over the past several decades, it has been known that a significant shift from the normal number of VMB colonies affects the integrity of the mucosal surface protective layer. The imbalance of VMB colonies and their effects on the vagina can cause an increased risk of sexually transmitted infections (STI) including bacterial vaginosis, vulvovaginal candidiasis, gonorrhoea, trichomoniasis, *Chlamydia trachomatis* infection, herpes simplex virus (HSV) infection, bacterial vaginosis infection, vulvovaginal candidiasis, gonorrhoea, trichomoniasis, *Chlamydia trachomatis* infection, herpes simplex virus (HSV) infection, human papillomavirus infection (HPV), and human immunodeficiency virus (HIV) infection.

Keywords: *Lactobacillus*, STI, vaginal microbiota

Introduction

The vagina is an ecosystem consisting of various species of microorganisms (microbiota) that are compatible with vaginal health.¹⁻³ The vaginal ecosystem includes a variety of species that become aerobic and anaerobic microorganisms.^{1,2} Aerobic and anaerobic microorganisms which are vaginal microbiota (VMB) have an important function in maintaining vaginal health and preventing sexually transmitted infections (STIs). Current research has found more than 50 species of microorganisms that exist in the vaginal canal.⁴

In the vagina of a healthy woman, the species of *Lactobacillus* is 70% of the normal VMB.^{3,5,6} The average number of *Lactobacillus* colonies that make up the vaginal ecosystem is 8x10⁷CFU / ml.⁴ *Lactobacillus* species are dominant in the vagina of healthy women in *L. crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii*. Other anaerobic microorganisms such as *Gardnerella*, *Atopobium*,

Mobiluncus, *Prevotella*, *Streptococcus*, *Ureaplasma*, and *Megasphaera* are also available in the vagina of healthy women.^{2,3,7,8} *Lactobacillus* is a Gram-positive, anaerobic, and member of lactic acid bacteria (LAB). Lactic acid bacteria produce lactic acid which plays a role in the bonding of vaginal acidity at pH <4, producing H₂O₂ and bacteriocin, modulating non-specific immune responses, and preventing colonization of microorganisms through competitive adhesion to the vaginal epithelium.¹³ The role of *Lactobacillus* in preventing colonization and growth of harmful microorganisms.^{5,7,8}

The composition of VMB that lives in each woman's vagina can be different and can change drastically in a short time in the same woman.^{2,9} The composition of VMB easily varies between ethnic or racial groups.^{2,9,10} Several studies have shown that this variation in VMB is related to genetic variation in the host.^{11,12}

Fluctuations in VMB composition can be caused by various endogenous and exogenous factors produced by hormones, menstrual cycles, social activities, antibiotic therapy, antifungals, use of oral contraceptives, contraceptives, vaginal douching, menopause, pregnancy, lactation, diabetes mellitus, stress, and immunosuppressive conditions.¹¹⁻¹³

Over the past several rounds, it was recognized that significant changes in the number of normal VMB colonies affected the integrity of the mucosal surface protective layer. Imbalance of VMB colonies and their effect on vaginosis that is caused by sexually transmitted infections (STI) due to bacterial vaginosis, vulvovaginal candidiasis, gonorrhoea, trichomoniasis, *Chlamydia trachomatis* infection, herpes simplex virus (HSV), human papillomavirus (HPV), human immunodeficiency virus (HIV).^{1,2,4}

The role of the VMB is very important in maintaining vaginal health. Research on the colonization of VMB that addresses infectious diseases continues to grow. These studies reveal an imbalance of VMB (dysbiosis) that can cause sexually transmitted infections (STIs). Therefore, improving knowledge about it can provide us with important knowledge about VMB and its effects on increasing STI disease.^{1,2}

Eubiosis of vaginal microbiota

Lower immunity female reproductive tract system

The lower female reproductive tract (FRT) consists of the ectocervix and vaginal canal that is coated in Type II mucosa. Type II mucosa in the vagina is covered by layered squamous epithelium without keratin which is continuously lubricated by cervicovaginal fluid (CVF). The composition of CVF consists of exfoliating epithelial cells, bacteria, and bacterial products.^{1,2,4,5} Squamous epithelial cells in the vagina have tight junctions between cells that allow the transport of small molecules such as viruses and the production of pathogenic microorganisms into the epithelial space. The structure of the vagina acts as a physical and chemical barrier to endogenous and exogenous factors.^{1,2,4,5}

In addition to the structure and CVF and VMB, the homeostasis of the vaginal ecosystem is also influenced by immune cells found in the vagina.^{1,2,4,5,7} In addition to acting as a physical barrier against pathogens, vaginal epithelial cells

produce cytokines and chemokines which induce leukocyte differentiation and mediate the inflammatory process.^{5,7,8}

The exact mechanism of *Lactobacillus* activity is unclear. The mechanism of *Lactobacillus* in the human vagina has been proven *in vivo*. In the vaginal lumen, *Lactobacillus* strains can directly inhibit pathogenic microorganisms by producing lactic acid, H₂O₂, bacteriocin, and other inhibiting agents. *Lactobacillus* can also maintain the integrity of the vaginal epithelium and compete with pathogenic microorganisms to bind to receptors on the vaginal epithelium thereby preventing other microbes from sticking and infecting vaginal epithelial cells. *Lactobacillus* also produces antimicrobial peptides (AMPs), namely defensins, secretory leukocyte protease inhibitors (SLPI), lysozyme, lactoferrin, and elafin which play a role in killing pathogenic microorganisms. Vaginal *Lactobacillus* can also capture viruses mediated by C-type lectin molecules by binding to glycoprotein virus antigens.^{1,2}

Pathogenic microorganisms will express pathogen-associated molecular patterns (PAMPs) that are recognized by the pattern recognition receptor (PRR) found in epithelial cells. Epithelial cells in FRT have a variety of pattern recognition receptors (PRR), including Toll-like receptors (TLRs) and NOD receptor receptors. Antigens from pathogenic microorganisms that are recognized by PRRs migrate to the lymph nodes to present antigens and activate T cells, then produce proinflammatory cytokines such as interleukin-6 (IL-6), IL-8, tumor necrosis factor- α (TNF- α), macrophage inflammatory protein-1 α (MIP-1 α) and MIP-1 β . Vaginal *Lactobacillus* can regulate the immune system.¹⁴ Several studies have explained that the dominant metabolite produced by the *Lactobacillus species* is lactic acid. Apart from lactic acid, other metabolites that are also produced in small amounts by the *Lactobacillus* bacteria are short-chain fatty acids (SCFAs). Short-chain fatty acids (SCFAs) act as an anti-inflammatory, but anti-inflammatory effects do not appear to be significant if they are present in small amounts. Current research shows that SCFAs in high concentrations (20 mM) can induce proinflammatory cytokines compared to low concentrations.¹⁵

Normal vaginal microbiota

Normal VMB describes bacterial species that are commonly found in healthy vaginal biotopes and are part of the vaginal ecosystem and play a role in vaginal homeostasis.^{1-3,5,16} The VMB can be

influenced by the ethnic background or race of a woman. Caucasian women are dominated by *L. iners* species, Asian women are dominated by *L. crispatus*, while the VMB of black women and Hispanic women are dominated by *L. jensenii*.¹

Overall, normal vaginal flora is dominated by various *Lactobacillus* species. *Lactobacillus* is known as "Döderlein's bacillus" which is a Gram-positive bacterium. More than 20 species of *Lactobacillus* have been found in the vagina of a premenopausal woman while a woman of childbearing age is generally dominated by one or two *Lactobacillus* species. The most common species of *Lactobacillus* found in the vagina of healthy women are *L. crispatus*, *L. jensenii*, *L. gasseri*, and *L. iners*.^{2,4,17}

Molecular and cultural study techniques have now found 581 bacterial species in the human VMB accompanied by the discovery of yeast namely *Candida albicans* approximately 25%.^{17,18} The vaginal bacterial species found are grouped into 10 phyla with the dominant phylum *Firmicutes* (phylum *Firmicutes* (39.1%, 227 bacterial species). Normal microbiota in the vagina of a healthy woman is dominated by *Lactobacillus* species which are included in the phylum *Firmicutes*.^{1,2,3,4,17}

Bacterial species that often cause sexually transmitted infections include *Gardnerella vaginalis* (*Actinobacteria*), *Neisseria gonorrhoeae* (*Proteobacteria*), *Haemophilus ducreyi* and *Prevotella* (*Firmicutes*), *Mycoplasma hominis* and *Ureaplasma urealyticum* (*Tenericutes*), *Treponema* (*Spirochaetes*), and *Chlamydia trachomatis* included in the *Chlamydiae* phylum.^{1,4,17,18}

Changes in vaginal pH and estrogen hormone fluctuations throughout the female reproductive stage

Maternal vaginal canal microbiota is a source of early colonization of infant microbiota born through vaginal delivery. In the first few weeks after birth, which is about two to four weeks, increased maternal estrogen hormone causes proliferation and thickening of the vaginal mucosal cells and increases glycogen production. Babies born at vaginal birth obtain VMB that resembles their own mother's VMB which is mainly dominated by *Lactobacillus* species. In contrast, infants born with caesarian section have VMB similar to those found on the surface of the skin which is dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*. This

phase does not last long after maternal estrogen is metabolized and estrogen levels decrease, vaginal epithelium begins to thin, and glycogen levels decrease increasing vaginal pH.^{2,5,14,19}

The prepubertal VMB is dominated by anaerobic microorganisms namely *E. coli*, diptheroids, and coagulase-negative *Staphylococci* with significantly lower glycogen levels. At puberty, increased estrogen levels encourage maturation, proliferation, and accumulation of glycogen in vaginal epithelial cells which are then metabolized to lactic acid by the *Lactobacillus sp.* This creates an acidic environment (pH 3.5-4.5) which is conducive to the growth of *Lactobacillus*.^{5,14,19}

In the adult life stage, glycogen levels increase due to increased estrogen levels. The degradation of glycogen to glucose by the *Lactobacillus sp.* causes a decrease in vaginal pH thereby preventing the growth of pathogenic bacteria.¹⁹⁻²⁰ Postmenopausal, estrogen levels decrease again, and there is a reduction in glycogen deposition so that there are a variety of microorganisms and increased vaginal pH. After menopause, *Lactobacillus* dominance decreases due to decreased estrogen levels.^{2,5,19,20}

Increased estrogen levels during pregnancy result in an increase in vaginal glycogen deposition which increases the proliferation of VMB predominantly *Lactobacillus*. Several studies have shown that menstruation significantly changes the diversity of VMB, which is about a 100-fold decrease in *L. crispatus* and an increase in *L. iners*, *G. vaginalis*, *P. bivia*, and *A. vaginae*. Normal vaginal acid pH in women of reproductive age is influenced by estrogen, glycogen, and *Lactobacillus*.^{2,5,19,20}

Vaginal microbiota dysbiosis

Dysbiosis is a condition where there are qualitative and quantitative changes in the composition, distribution, and metabolic activity of microbes that will cause adverse effects on the host. This VMB dysbiosis increases susceptibility to genital disease.^{5, 21-23}

Factors affecting vaginal microbiota dysbiosis

Sexual intercourse

Sexual intercourse has a minimal effect on vaginal colonization of *Lactobacillus*. A study showed a significant increase in the colonization of

Enterococcus, *E. coli*, and *B-Streptococcus* bacteria after vaginal intercourse.²¹ These three microorganisms are associated with sexual relations in an anogenital manner. This results in a decrease in *Lactobacillus* colonization thereby increasing vaginal pH.^{5,21}

Stress

A molecular engineering study had been conducted to identify the growth of VMB in stressful conditions. In this study, it was shown that the decrease in the number of *Lactobacillus* under stress had a relationship with the HPA axis (hypothalamic pituitary adrenal).²⁴

Use of vaginal products and contraception

Many young women use vaginal products such as lubricants or lubricants, contraceptives, and douches. Lubricant products found in some condoms contain nonoxynol-9 (N-9) chemicals that can kill sperm or stop its movement. The use of N-9 can increase *E. coli* colonization.^{5,21-25}

The impact of contraception on the balance of vaginal microbiota is still under study.^{5,21-25} In oral contraceptives depot medroxyprogesterone acetate (DMPA) produces hypoestrogenic status known to cause a decrease in *Lactobacillus* colonization thereby reducing the hydrogen peroxide density produced by *Lactobacillus*, thinning of the vaginal epithelium, and loss of glycogen.^{5,21} Cooper-IUD also causes a decrease in *Lactobacillus* colonization. Several studies that have examined the use of douches show that vaginal douching activity can affect normal VMB colonization.^{5,21,22}

The use of oral antibiotics

Antimicrobial agents used to treat nongenital and genital infections can affect the vaginal microbial ecosystem of *Lactobacillus*. *Lactobacillus* is susceptible to beta-lactam antibiotics such as amoxicillin and cephalosporin, which are often used to treat genital tract infections.^{1, 5, 23}

Smoking

Research shows that smoker women have an increase in biogenic amines when compared to nonsmoker women. This biogenic amine plays a role in the proliferation of anaerobic bacteria, disrupting the balance of the VMB. Other results also showed that smoking in women significantly decreased the amount of *Lactobacillus* colonization.^{5,23,25}

Vaginal microbiota and sexually transmitted infections

Bacterial Vaginosis

Bacterial vaginosis (BV) is a VMB dysbiosis, especially in women of reproductive age where there is an increase in anaerobic bacteria including *Gardnerella* sp., *Atopobium*, *Mobiluncus*, *Prevotella*, *Streptococcus*, *Ureaplasma*, *Megasphaera*.^{1,26}

During BV, there is an increase in various anaerobic bacteria which is characterized by increased concentrations of SCFA and amines accompanied by an increase in vaginal pH > 4.5. Diverse and large amounts of anaerobic bacteria can damage the epithelial barrier and reduce mucin. Short-chain fatty acids (SCFAs) can produce pro-inflammatory cytokines (IL-6, IL-1 β , TNF α , IL-8) and chemokines (RANTES, MIP-1 β), as well as several antimicrobial peptides (hBD-2, defensins).^{1,26}

Vulvovaginal candidiasis

Vulvovaginal candidiasis is an infection caused by *Candida albicans*.^{1,2,28} Colonization of *Candida albicans* in the vaginal canal is influenced by estrogen levels and colonization factors. *Candida albicans* has an estrogen-binding protein (EBP) that binds to the estrogen receptor in the cytosol. The ligand-EBP interaction will stimulate the colonization of *C. albicans*. High estrogen levels also increase the accumulation of glycogen in vaginal epithelial cells that play a role in providing a carbon source for the growth of *C. albicans*. Estrogen can also induce the expression of soluble heat-shock proteins in *C. albicans* which causes germ tube formation which acts as spore formation.^{1,2,27,28}

Gonorrhoeae

During the initial infection, *Neisseria gonorrhoeae* bind to vaginal epithelial cells through type IV pili and then replicate and form a microcolony that competes with *Lactobacillus* sp. In the vaginal ecosystem which has decreased colonization of *Lactobacillus* sp. can reduce the competitiveness of *Lactobacillus* sp. on epithelial cells thereby increasing the colonization of *N. gonorrhoeae*.^{1,29}

Trichomoniasis

Trichomoniasis is caused by *Trichomonias vaginalis*, a pathogenic parasite that is transmitted mainly through sexual contact. VMB dysbiosis

characterized by a decrease in the number of *Lactobacillus* can reduce the competitiveness of *Lactobacillus* against *Trichomonas vaginalis* in vaginal epithelial cells. These conditions led to an increase in the colonization of *Trichomonas vaginalis*.^{2,29-31}

Chlamydia infection

Chlamydia infection is an infection caused by *Chlamydia trachomatis*.^{2,32,33} Chlamydial infection begins with attachment to vaginal epithelial cells in a highly contagious form called the elementary body (EB). The elementary body differentiates and replicates within the host cell in the form of small vesicles. The survival and replication of Chlamydia Trachomatis are very dependent on the host epithelial cell. An imbalance of the vaginal ecosystem characterized by a decrease in the number of *Lactobacillus* colonies provides a great opportunity for attachment between Chlamydia Trachomatic and vaginal epithelial cells.^{2,32,33}

Herpes simplex virus (HSV), human papillomavirus (HPV), human immunodeficiency virus (HIV)

Herpes simplex type 2 (HSV type 2) or genital herpes and human immunodeficiency virus (HIV) are sexually transmitted infections with biological mechanisms that are not yet fully understood.^{17,34,35} *Lactobacillus* strains can directly inhibit viral microorganisms such as HIV by producing lactic acid, H₂O₂, bacteriocin, and other inhibiting agents (Figure 1). The vaginal *Lactobacillus* strain can also capture viruses mediated by the C-type lectin molecule by binding to the glycoprotein viral antigen so that it inhibits viral replication (Figure 5). Current research finds a mechanism of viral infection in the vagina such as HSV and HPV through the role of IL-33 as an antiviral immunity in the vaginal mucosa. IL-33 plays a role in blocking migration from CD 8 T cells and inhibiting IFN-pro proinflammatory cytokines.^{17,34,35}

Conclusion

Lactobacillus sp. is a microorganism that has a very important function in maintaining the health of the vaginal canal and protecting it from sexually transmitted infections. Fluctuations in the composition of VMB can be influenced by various factors namely estrogen hormones, menstrual cycles, sexual relations, use of vaginal products and contraception, use of antibiotics, and smoking. VMB dysbiosis can increase the risk of

sexually transmitted infections (STI) such as bacterial vaginosis, vulvovaginal candidiasis, gonorrhea, trichomoniasis, chlamydia infections, herpes simplex virus (HSV), human papillomavirus (HPV) infections, and human immunodeficiency virus (HIV) infections.

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