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Kadın Genital Sistemi Mikrobiyomu: Derleme

The Female Genital Tract Microbiome: a review

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ÖZ

İnsan mikrobiyomu, mikroorganizmalar ve genetik materyalleri içeren karmaşık bir ekosistem olup insan sağlığı için hayati önem taşıyan fizyolojik süreçleri derinden etkiler. İnsan vücudundaki çeşitli bölgeler arasında, kadın genital sistemi çeşitli mikrobiyal toplulukları barındırır ve bu da vajinal mikrobiyata olarak bilinir. Bu mikrobiyata, vajinal sağlığı korumak ve enfeksiyonları önlemek için hayati bir rol oynar. Bu incelemede, jinekolojik hadiseler ile vajinal mikrobiyatanın karmaşık ilişkisini ele aldık; bunlar arasında bakteriyel vajinoz, insan papillomavirüsü (HPV) enfeksiyonu, servikal neoplazi, endometrial kanser, over kanseri, erken doğum ve kısırlık bulunmaktadır. Vajinal mikrobiyatadaki değişiklikler, özellikle koruyucu Lactobacillus türlerinin azalması ve anaerobik organizmaların artması şeklindeki mikrobiyal dengesizlik, bu durumlar için daha yüksek riskle ilişkilendirilmiştir. Özellikle bakteriyel vajinoz, HPV enfeksiyonunun kalıcılığı ve neoplastik gelişim ile ilişkilendirilen bir dengesizlik dikkat çekmektedir. Ayrıca, gebelik sırasında vajinal mikrobiyotun değişimleri, doğum sonuçları üzerinde etkilidir ve floradaki lactobacillis azlığı, kadınları erken doğuma yatkın hale getirir. Dahası, anormal vajinal flora, kadın kısırlığıyla ilişkilendirilmiş olup embriyo yerleşimi, tüplerdeki faktörler ve gebelik sonuçlarını etkiler. Vajinal mikrobiyatanın jinekolojik durumları üzerindeki rolünün anlaşılmasında ilerleme olmasına rağmen, özellikle randomize kontrollü çalışmalar olmak üzere daha fazla araştırma yapılması, temel mekanizmaları netleştirmek ve hedefe yönelik tedaviler geliştirmek için gereklidir.

Anahtar Kelimeler: Vajinal mikrobiyata, Mikrobiyom, Bakteriyel Vajinoz, Jinekolojik Kanser

ABSTRACT

The human microbiome, a complex ecosystem consisting of microorganisms and their genetic material, profoundly impacts physiological processes crucial for human health. Among various niches within the human body, the female genital tract harbours a diverse microbial community, known as the vaginal microbiota, which plays a pivotal role in maintaining vaginal health and preventing infections. This review explores the intricate relationship between the vaginal microbiota and gynaecological conditions, including bacterial vaginosis, human papillomavirus (HPV) infection, cervical neoplasia, endometrial cancer, ovarian cancer, preterm birth, and infertility. Changes in the composition of the vaginal microbiota, known as dysbiosis, have been associated with a higher risk of these conditions. Notably, dysbiosis characterized by a reduction in protective Lactobacillus species and an increase in anaerobic organisms is associated with bacterial vaginosis, HPV infection persistence, and neoplastic development. Furthermore, alterations in the vaginal microbiota during pregnancy have implications for gestational outcomes, with a low frequency of lactobacilli predisposing women to preterm birth. Moreover, abnormal vaginal flora has been implicated in female infertility, affecting embryo implantation, tubal factors and pregnancy outcomes. Although there has been progressing in understanding the role of the vaginal microbiome in gynaecological health, additional research, particularly randomized controlled trials, is necessary to clarify the underlying mechanisms and devise targeted therapies.

Keywords: Vaginal microbiota, Microbiome, Bacterial Vaginosis, Gynecological Cancer

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The Microbiome

The human microbiome is an ecosystem teeming with microorganisms, their genetic material, and the chemical environment in which they exist within the human body. The hidden world of microbiota holds significant importance in influencing physiological processes essential for human health, notably by reinforcing the immune system and optimizing nutritional intake, while these microscopic inhabitants forge a symbiotic bond with their human hosts, establishing a mutually beneficial relationship. (1) The immune system stands at the forefront of this symbiotic relationship, drawing upon the diversity and equilibrium of the microbiome to mount effective defences against pathogenic threats. The structural composition of microbial communities within the microbiota plays a pivotal role in determining an individual's health status. (2) Next-generation sequencing (NGS) techniques, along with methods such as 16S rRNA gene analysis, have enabled the detailed examination of microbial structures that cannot be cultivated using culture-based microbiological methods. These techniques allow for the direct determination of the genetic makeup of microorganisms, facilitating the characterization of microbial communities from various environmental samples. This enables a more comprehensive understanding of microbial diversity and functions that cannot be achieved through traditional culture methods. (3)

The female genital tract (FGT) microbiome

The female genital microbiota, consisting of microorganisms inhabiting the vagina, vulva, and adjacent areas, plays a crucial role in maintaining vaginal health and preventing infections.

The vaginal microbiota, comprising approximately 9% of the total human microbiota, represents a dynamic ecosystem influenced by a multitude of factors. (4)Variations in its composition and diversity are intricately linked to hormonal status, sexual activity patterns, and individual hygiene practices. This microbial community acts as a shield, safeguarding the host vagina against the infiltration of potentially pathogenic microbes responsible for conditions such as bacterial vaginosis, urinary tract infections, candida infections, and various sexually transmitted diseases (STDs). (5)

The normal vaginal flora, reproductive-aged woman comprises a diverse array of aerobic, facultative anaerobic, and obligate anaerobic species. Among these, anaerobic bacteria predominate, outnumbering aerobic species by approximately 10 to 1. (6) In the vaginal flora, more than 20 different strains of Lactobacillus are found, which are considered the dominant factor in maintaining a vaginal pH between 4 and 4.5 by producing lactic acid, fatty acids, and other organic acids. This acidic environment provides a protective effect against pathogenic conditions. Glycogen, found in healthy vaginal mucosa, serves as a nutrient source for various species within the vaginal ecosystem and is metabolized into lactic acid . (7) The glycogen content within vaginal epithelial cells typically decreases following menopause and is minimal during childhood. Consequently, postmenopausal women not undergoing estrogen replacement therapy and young girls exhibit a lower prevalence of Lactobacillus species and reduced acid production compared to reproductive-aged women. In addition to lactobacilli, the vaginal ecosystem harbors more than 50 non-pathogenic microbial species. (8) This diverse microbial community forms a complex symbiotic relationship within the vaginal environment, contributing to its overall health and functionality.(9, 10)

Bacterial Vaginosis (BV)

Bacterial vaginosis (BV) is a prevalent clinical syndrome characterized by an imbalance in the vaginal flora, particularly marked by an overrepresentation of anaerobic species. This imbalance leads to a depletion of protective Lactobacillus species and an increase in facultative and anaerobic organisms within the vaginal microenvironment. Notable anaerobic species associated with BV include Gardnerella, Prevotella, Mobiluncus, and Bacteroides. Clinically, BV manifests through symptoms such as foul-smelling vaginal discharge, burning sensation during urination, and itching around and outside the vagina.(11, 12)

In 2011, Ravel and colleagues use of next-generation sequencing (NGS) techniques to analyze bacterial 16S rRNA genes and characterize the vaginal microbiota (VMB) of 396 ethnically diverse reproductive-age women. Their study introduced a clustering analysis method, which categorized individuals' vaginal microbial compositions into one of five distinct "community state types" (CSTs). CST I, II, III, and V were identified by the dominance of specific Lactobacillus species—crispatus, gasseri, iners, and jensenii, respectively—exhibiting low species diversity and evenness. In contrast, CST IV lacked Lactobacillus spp. and was instead enriched with strict anaerobic species

commonly associated with bacterial vaginosis. (3) Additionally, molecular ribosomal RNA gene sequencing techniques have further advanced the classification of specific bacteria within vaginal flora ecosystems, enabling researchers to quantify the risk of BV associated with CST groups. BV is associated with numerous adverse health outcomes, including an elevated risk of preterm birth, low birth weight, acquisition of sexually transmitted infections (STIs) such as HIV, and increased susceptibility to chlamydial and gonococcal infections. Additionally, women with BV are at risk of developing gynecologic complications such as vaginitis, endometritis, pelvic inflammatory disease (PID), and acute pelvic infections following pelvic surgery, particularly hysterectomy.

Gynecological Cancers

HPV Infection and its Relationship with the Vaginal Microbiome

Human Papillomavirus (HPV) the majority of cervical neoplasia, along with a notable portion of vulvar, vaginal, and anal squamous neoplasias. Vaginal microbiome might play a role in influencing the progression of HPV infection and subsequent neoplastic development. In meta-analyses of primarily cross-sectional studies, the presence of bacterial vaginosis (BV) has been found to be associated with higher rates of HPV infection (12 studies; odds ratio (OR) 1.43, 95% CI 1.11 to 1.84). This suggests that a diverse microbiome lacking Lactobacillus species may contribute to the persistence of HPV. Additionally, there is evidence indicating that HPV persistence is more likely in individuals with an altered microbiome. Although there is variability among studies regarding the specific anaerobic species related to HPV presence and cervical preinvasive disease, there is a consensus that both viral persistence and preinvasive lesions are linked to a decrease in Lactobacillus species and an increase in vaginal microbiome diversity. Results derived from a network meta-analysis comprising 11 studies conducted in 2019 indicated that individuals with a vaginal microbiome lacking of Lactobacillus species or characterized by dominance of L. İners (CST-3) had three to five times higher odds of HPV positivity and two to three times higher odds of high-risk HPV (hrHPV) infection and cervical dysplasia or cancer when compared to those with a microbiome dominated by Lactobacillus crispatus (CST-1).

NGS methods were not utilized in most studies. However, in the analysis of data obtained from the Healthy Twin Study within the scope of the Korean Genome Epidemiology Study, the relationship between NGS, vaginal flora, and HPV infection was demonstrated for the first time. In this study involving 68 women, 23 tested positive for HPV, while 45 tested negative. Comparatively, HPV-positive individuals exhibited higher microbial diversity with a reduced proportion of Lactobacillus spp.. (13) Subsequent studies have consistently shown that as the complexity of normal vaginal microbiota increases and the abundance of Lactobacillus species decreases, there is a consistent trend of increased transient or persistent HPV infection. (14, 15) One of the most significant investigations in this context involved a cohort of 169 women in the UK, comprising 20 normal controls, 52 with low-grade squamous intraepithelial lesion (LSIL), 92 with high-grade squamous intraepithelial lesion (HSIL), and five with invasive cervical cancer. This study revealed a correlation between the increasing severity of cervical intraepithelial neoplasia (CIN) and heightened vaginal microbiota (VMB) diversity. Particularly noteworthy was the observation that the prevalence of CST-4 increased two-, three-, and four-fold in cases of low-grade CIN, high-grade CIN, and invasive cervical cancers. (16)

In articles discussing the mechanism by which the increase in Lactobacillus abundance affects transient or persistent HPV infection, it is suggested that the pH-lowering effect of Lactobacillus, coupled with their bacteriocin production, may positively contribute to the epithelial barrier function during the passage of the HPV virus from basal keratinocytes. However, studies in this area are inadequate, and there are many aspects that require further evidence and confirmation. (17, 18)

In light of this information, it becomes evident that the vaginal microbiota plays a crucial role in both acquiring and maintaining HPV in the human vagina, as well as in the subsequent development and progression of CIN. However, to fully understand the influence of vaginal microbiota composition on these disease outcomes, additional longitudinal studies are imperative. As evidence on this topic continues to accumulate, the potential for developing novel treatment methods becomes increasingly promising.

Endometrial cancer and its Relationship with the Vaginal Microbiome

Endometrial cancer is influenced by various factors such as obesity, hormonal imbalances, diabetes, and metabolic syndrome, all of which have the potential to induce alterations in the microbiota. While the majority of endometrial cancers ex-

hibit estrogen-dependent proliferation, the exact carcinogenic mechanisms are not entirely understood, except for specific mutations in oncogenes and tumor suppressor genes like p53. Environmental and host factors, such as obesity, diabetes mellitus, and hormonal changes, do not fully explain the tumorigenic mechanism. It has been observed that endometrial cancer patients often exhibit low levels of lactobacilli across all stages of the disease. (19) Several studies have investigated the endometrial and vaginal microbiota in relation to endometrial cancer. Although there is some disagreement among these studies regarding the diversity of endometrial microbiota in the presence of malignancy, there is a consensus regarding the increased prevalence of anaerobic bacteria, including Atopobium, Porpyromas, Prevotella, and Pseudomonas species. However, variations exist across different studies.(20)

Ovarian cancer and its Relationship with the Vaginal Microbiome

Ovarian cancer is one of the most lethal gynecological malignancies,therefore the critical importance of prevention strategies and early diagnosis. Chronic infections with sexually transmitted pathogens and inflammation in the genital tract have been implicated in ovarian tumor development. Pilot studies have detected various bacteria in ovarian cancer tissues, suggesting a potential link with inflammation; however, the causal relationship between microbiota and ovarian cancer remains uncertain. hese microorganisms may potentially induce carcinogenesis through direct or indirect mechanisms, with the highly anoxic tumor microenvironment possibly facilitating the recruitment and growth of anaerobic microorganisms. Additional validation of the link between pathogenic microorganisms, chronic inflammation, and ovarian cancer requires extensive epidemiological studies encompassing large patient cohorts and longitudinal research designs. (21)

Temporal Dynamics of Vaginal Microbiota During Pregnancy and Its Impact on Gestational Outcomes

Globally, the prevalence of preterm birth (PTB) is estimated at around 10 percent, varying from 5 percent in certain regions of Europe to 18 percent in parts of Africa. Each year, roughly 15 million infants are born preterm, with numbers ranging from 12 to 18 million.(22) Predicting and preventing preterm birth is highly important in contemporary healthcare. Pregnancy induces significant alterations in the composition of the vaginal microbiome, characterized by increased stability and reduced diversity. Lactobacillus predominates in the microbial community, and the presence of a Lactobacillus-deficient vaginal community state type 4 (CST 4) is associated with preterm delivery. Furthermore, individuals with CST 4 and increased levels of Gardnerella or Ureaplasma have a higher risk of spontaneous preterm birth. (23) Contradictory findings by Romero et al. challenge the causal relationship between abnormal vaginal flora and preterm birth.(24) Treating bacterial vaginosis (BV) does not decrease the rates of PTB in low-risk patients. (25) In summary, the diversity of the vaginal microbiome appears to influence the risk of preterm birth, with women having a low abundance of lactobacilli being at a higher risk compared to those with a microbiome predominantly dominated by L. crispatus. (26, 27)

Vaginal microbiome and infertility

Female infertility is a multifactorial condition with various potential contributors, among which abnormal vaginal flora has appear as a significant factor. Studies have indicated that women with idiopathic infertility are more likely to present abnormal vaginal flora. (28) The vaginal microbiome plays role during embryo implantation and subsequent pregnancy outcomes. Additionally, infections in the reproductive tract, such as BV, are known to contribute to infertility, especially tubal infertility. (29) Chronic inflammation resulting from BV may lead to tubal adhesions, impairing fertility. Studies has been shown that the presence of hydrogen peroxide-producing Lactobacillus crispatus in the vaginal environment can increase the success rate of embryo implantation and live birth.(4) Vaginal microbiota balance could potentially reduce infertility risks. (28) A need for more extensive studies focusing on infertility and the microbiota. Further research is imperative to comprehensively understand the underlying mechanisms and to devise improved treatment strategies for female infertility.

CONCLUSIONS

The vaginal microbiome undergoes variations throughout different stages of the female reproductive and post-reproductive life cycles. These variations are influenced by environmental factors, physiological conditions, and life events such as puberty, menopause, and pregnancy. Vaginal dysbiosis, characterized by an imbalance in the vaginal microbiota, can significantly increase the risk of various health conditions, including sexually transmitted diseases, gynecological cancers, preterm birth, and infertility. This review article provides a comprehensive insight into the relationship between the microbiota of the female reproductive tract and gynecological infections, such as bacterial vaginosis, HPV infection, pre-invasive lesions of the cervix, cervical, endometrial, and ovarian cancers, preterm birth, and infertility, from a clinician's perspective. Understanding the vaginal microbiota suggests its potential involvement in a wide range of clinical conditions, prompting clinicians to consider microbiota-related factors in patient management and research design. While the concept of the vaginal microbiota underlying various idiopathic conditions is intriguing, conclusive evidence requires extensive randomized controlled trials.

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