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INDIVIDUALIZATION OF ART PROTOCOLS IN PATIENTS WITH DIFFERENT OVARIAN RESERVE

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ABSTRACT

Infertility remains one of the most important challenges in modern reproductive medicine and requires an individualized approach to improve the effectiveness of assisted reproductive technologies (ART). The aim of this study was to evaluate ART outcomes in patients with different ovarian reserve levels and to determine the role of personalized treatment protocols. This prospective study included 60 infertile women treated at the “Beshik” Reproductive Medicine Clinic (Samarkand, Uzbekistan) during 2025–2026. The participants were divided into two groups according to ovarian reserve: normal ovarian reserve (n=30) and diminished ovarian reserve (n=30). Ovarian reserve was assessed using anti-Müllerian hormone levels and antral follicle count, and all patients were additionally stratified according to the POSEIDON concept. Although patients with diminished ovarian reserve demonstrated lower numbers of retrieved oocytes and less favorable embryological outcomes, individualized ovarian stimulation protocols allowed satisfactory rates of oocyte maturation, fertilization, and blastocyst formation to be achieved. The findings indicate that personalization of ART protocols based on ovarian reserve assessment and POSEIDON stratification contributes to improved reproductive outcomes.

Keywords: infertility, assisted reproductive technologies, IVF, ICSI, ovarian reserve, AMH, POSEIDON, personalization

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ИНДИВИДУАЛИЗАЦИЯ ПРОТОКОЛОВ ВРТ У ПАЦИЕНТОК С РАЗЛИЧНЫМ ОВАРИАЛЬНЫМ РЕЗЕРВОМ

АННОТАЦИЯ

Бесплодие является одной из наиболее актуальных проблем современной репродуктивной медицины и требует индивидуализированного подхода для повышения эффективности вспомогательных репродуктивных технологий (ВРТ). Целью исследования явилась оценка результатов ВРТ у пациенток с различным овариальным резервом и определение значения

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VAGINAL MICROBIOCENOSIS IN WOMEN WITH CERVICAL DYSPLASIA: A COMPREHENSIVE REVIEW OF HPV-POSITIVE AND HPV-NEGATIVE PATIENTS

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ABSTRACT

Cervical dysplasia (cervical intraepithelial neoplasia, CIN) is a premalignant condition strongly associated with persistent infection by high-risk human papillomavirus (HPV). However, HPV-independent pathways also exist, suggesting the role of additional cofactors such as vaginal microbiocenosis. This review provides an expanded analysis of vaginal microbiota in HPV-positive and HPV-negative cervical dysplasia, focusing on microbial composition, immune interactions, and clinical implications

Keywords: Cervical dysplasia; HPV; vaginal microbiota; microbiocenosis; CIN; Lactobacillus; dysbiosis.

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ВАГИНАЛЬНЫЙ МИКРОБИОЦЕНОЗ У ЖЕНЩИН С ДИСПЛАЗИЕЙ ШЕЙКИ МАТКИ: КОМПЛЕКСНЫЙ ОБЗОР HPV-ПОЗИТИВНЫХ И HPV-НЕГАТИВНЫХ ПАЦИЕНТОК

АННОТАЦИЯ

Дисплазия шейки матки (цервикальная интраэпителиальная неоплазия, CIN) является предраковым состоянием, тесно связанным с персистирующей инфекцией онкогенных типов вируса папилломы человека (HPV). Однако существуют и HPV-независимые механизмы развития заболевания, что указывает на роль дополнительных кофакторов, таких как вагинальный микробиоценоз. В данном обзоре представлен расширенный анализ вагинальной микробиоты у HPV-позитивных и HPV-негативных пациенток с дисплазией шейки матки с акцентом на микробный состав, иммунные взаимодействия и клиническое значение.

Ключевые слова:дисплазия шейки матки; HPV; вагинальная микробиота; микробиоценоз; CIN; Lactobacillus; дисбиоз.

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БАЧАДОН БЎЙНИ ДИСПЛАЗИЯСИ БЎЛГАН АЁЛЛАРДА ВАГИНАЛ МИКРОБИОЦЕНОЗ: HPV-МУСБАТ ВА HPV-МАНФИЙ БЕМОРЛАРДА КОМПЛЕКС ТАҲЛИЛ

АННОТАЦИЯ

Бачадон бўйни дисплазияси (цервикал интраэпителиал неоплазия, CIN) — бу олдиндан саратонига олиб келувчи ҳолат бўлиб, юқори хавфли инсон папиллома вируси (HPV) инфекциясининг узоқ сақланиши билан чамбарчас боғлиқ. Бироқ, HPVга боғлиқ бўлмаган механизмлар ҳам мавжуд бўлиб, бу қўшимча омиллар, жумладан вагинал микробиоценознинг аҳамиятини кўрсатади. Ушбу обзор мақолада HPV-мусбат ва HPV-манфий дисплазияли беморларда вагинал микробиотанинг кенгайтирилган таҳлили келтирилган бўлиб, микроб таркиби, иммун ўзаро таъсирлар ва клиник аҳамиятга алоҳида эътибор қаратилган.

Калит сўзлар:бачадон бўйни дисплазияси; HPV; вагинал микробиота; микробиоценоз; CIN; Lactobacillus; дисбиоз.

Introduction: Cervical intraepithelial neoplasia (CIN) is a precursor to cervical cancer and is primarily linked to persistent HPV infection, particularly high-risk types such as HPV-16 and HPV-18. However, not all HPV infections result in dysplasia, and some dysplastic lesions occur in HPV-negative women, highlighting the importance of additional cofactors including vaginal microbiota [1].The normal vaginal microbiota is dominated by Lactobacillus species, which maintain acidic pH and protect against pathogens [2]. These include L. crispatus, L. jensenii, L. gasseri, and L. iners.Vaginal microbiota is categorized into CSTs, with CST I (L. crispatus) being the most protective, while CST IV represents dysbiosis with anaerobic dominance [3].Dysbiosis leads to chronic inflammation, cytokine imbalance, and reduced antiviral defense, promoting HPV persistence [6]**.**

Cervical intraepthelial neoplasia, or CIN, is the term for abnormal cells on the cervix which are at risk of developing into cervical cancer. Persistently infected women with high-risk types of human papillomavirus, especially HPV-16 and 18, are most likely to develop CIN. Not every woman whose cervix contains HPV will see changes in her cervix and several women who have cervical changes will not test positive for the presence of HPV. CIN may also develop in women with a different form of vaginal microbiome [1].Bacterial species that are part of the normal vaginal flora, such as Lactobacillus species, will dominate the vaginal flora; amongst these types of bacteria are Lactobacillus crispatus, Lactobacillus jensenii, Lactobacillus gasseri, and Lactobacillus iners, all of which help to create an acid environment and can also offer protection from pathogenic bacteria [2]. Community State Types are a way to describe the classification of a person’s vaginal microbiota. Of these, Lactobacillus crispatus-dominated vaginal microbiota has been shown to be the healthiest and therefore offers the most protection to the individual. In contrast, polymicrobial anaerobic communities are linked to dysbiosis and disease. (3).Women who were HPV positive and were diagnosed with cervical dysplasia showed many differences in their vaginal microbiome compared to women who were HPV negative. These differences include decreased levels of Lactobacillus, increased diversity of microbes, and increased levels of anaerobic bacteria such as Gardnerella vaginalis, Atopobium vaginae, and Prevotella sp. (4,5).These changes may contribute to the continued inflammation, increased production of pro-inflammatory cytokines, decreased epithelial barrier function, and decreased immune responses that facilitate the continued presence of HPV and the progression of cervical lesions. (6In comparison to HPV-positive, HPV-negative cervical dysplasia is typically characterized by a relatively stable vaginal microbiome with a predominance of Lactobacillus and lower levels of inflammation, though mild dysbiosis may occur in some instances [7].The vaginal microbiome plays an important role in modulating the immune response through

regulation of cytokine production2, maintenance of epithelial integrity, and susceptibility to viral infection such as HPV [8].The existence of dysbiotic microbiomes may help support persistent infection as well as assist in integrating HPV into the host genome, both of which are necessary events in the progression of cervical cancer [9].Additionally, microbial metabolites and alterations in vaginal pH may both affect epithelial cell proliferation and lead to dysplastic changes in the cervix [10].

As a result, evaluating vaginal microbiome can provide important clinical tools for assessing health and disease, as well as a potential marker for disease progression, and assist in developing treatment approaches like probiotics to regain Lactobacillus predominance and improve cervical health outcomes. Cervical intraepithelial neoplasia (CIN) encompasses a range of premalignant alterations to cervix/uterine cervix epithelium, and is a well-established risk for developing invasive cervical cancer; the majority of patients with CIN are found to have HPV types with a high-risk for cervical cancer persistence, with the low-risk HPV types not contributory to the risk for CIN; yet, it is important to note that mere presence of an HPV infection does not guarantee development of CIN; many women develop and resolve their HPV infection naturally without ever showing any evidence of CIN; additionally, there are cases of CIN in women who have tested negative for HPV infection, which demonstrates the need to consider other variables such as vaginal microbiome, local immune response, hormonal levels, and environmental exposures when developing interventions to reduce risk of CIN and subsequently, cervical cancer.

The vaginal microbiota is a dynamic and complex ecological system composed of a variety of microorganisms that exist in a symbiotic relationship with the host, and in healthy reproductive-age women, it is predominantly colonized by Lactobacillus species such as Lactobacillus crispatus, Lactobacillus jensenii, Lactobacillus gasseri, and Lactobacillus iners, which are essential for maintaining vaginal homeostasis through the production of lactic acid, hydrogen peroxide, and antimicrobial peptides, thereby sustaining an acidic pH environment (typically between 3.8 and 4.5) that inhibits the growth of pathogenic microorganisms and protects the cervical epithelium from infection and inflammation [2].

The structure of the vaginal microbiota has been categorized into community state types (CSTs), where CST I, dominated by Lactobacillus crispatus, is considered the most stable and protective, while CST II, III, and V are dominated by other Lactobacillus species with varying degrees of protective capacity, and CST IV is characterized by a polymicrobial anaerobic community with reduced Lactobacillus abundance and increased microbial diversity, which is commonly associated with bacterial vaginosis and pathological conditions, including increased susceptibility to sexually transmitted infections and cervical dysplasia [3].In women with HPV-positive cervical dysplasia, numerous studies have demonstrated a strong association with vaginal dysbiosis, characterized by a significant reduction in Lactobacillus species and a concomitant increase in anaerobic and facultative anaerobic bacteria such as Gardnerella vaginalis, Atopobium vaginae, Prevotella spp., Sneathia spp., and Mobiluncus spp., leading to increased microbial diversity and instability of the vaginal ecosystem, which creates a favorable environment for viral persistence and progression of cervical lesions [4,5].This dysbiotic state contributes to the pathogenesis of cervical dysplasia through multiple mechanisms, including the induction of chronic low-grade inflammation, increased production of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-alpha, disruption of epithelial barrier integrity, and impairment of innate and adaptive immune responses, particularly the reduction of interferon-mediated antiviral activity, all of which facilitate HPV persistence, viral genome integration into host cells, and progression toward higher-grade lesions [6].Furthermore, not all Lactobacillus species confer equal protection, as Lactobacillus crispatus is associated with a stable and protective vaginal environment, whereas Lactobacillus iners is often found in transitional or dysbiotic states and may coexist with pathogenic bacteria, thereby providing less effective protection against HPV infection and persistence, which highlights the importance of microbial composition rather than merely the presence of Lactobacillus species [5].In contrast, HPV-negative cervical dysplasia presents a different microbiological profile, as these patients generally exhibit a more stable vaginal microbiota with a higher prevalence of Lactobacillus-dominated communities, lower microbial diversity, and less pronounced inflammatory responses,

although mild alterations in microbiota composition may still occur, suggesting that non-viral mechanisms such as hormonal imbalance, mechanical irritation, chronic nonspecific inflammation, or immune dysregulation may contribute to epithelial abnormalities in the absence of HPV infection [7].

The interaction between vaginal microbiota and cervical epithelium is mediated through complex immunological and biochemical pathways, where beneficial bacteria play a key role in maintaining mucosal immunity by stimulating the production of anti-inflammatory cytokines, enhancing epithelial barrier function, and preventing pathogen adhesion, while dysbiosis leads to immune dysregulation, increased susceptibility to infection, and a microenvironment conducive to carcinogenesis [8].Additionally, alterations in microbial metabolism can result in the production of bioactive compounds and enzymes that influence vaginal pH, degrade protective mucus layers, and generate potentially carcinogenic metabolites, thereby promoting epithelial cell proliferation, DNA damage, and progression of dysplastic changes, further emphasizing the role of microbiocenosis in cervical pathology [10].The persistence of HPV infection, which is a critical factor in the development of high-grade cervical lesions, is strongly influenced by the state of the vaginal microbiota, as dysbiotic conditions facilitate viral entry, replication, and integration into the host genome, whereas a Lactobacillus-dominated microbiota enhances viral clearance and reduces the risk of progression to malignancy, highlighting the potential of microbiota-targeted interventions in the prevention and management of cervical dysplasia [9].From a clinical perspective, the assessment of vaginal microbiocenosis represents a promising diagnostic and prognostic tool, as specific microbial patterns may serve as biomarkers for HPV persistence, disease progression, and treatment response, and therapeutic strategies aimed at restoring normal microbiota, including the use of probiotics, prebiotics, and targeted antimicrobial therapy, have shown potential in improving vaginal health, enhancing immune function, and reducing the risk of cervical disease progression, although further large-scale studies are needed to establish standardized treatment protocols and confirm long-term efficacy [11].

Conclusion:HPV-positive cervical dysplasia is strongly associated with vaginal dysbiosis, whereas HPV-negative cases tend to maintain microbial balance. Vaginal microbiocenosis plays a critical role in disease progression and represents a promising target for diagnostics and therapy.

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