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Роль цервиковагинальной микробиоты в возникновении плоскоклеточных интраэпителиальных поражений высокой степени злокачественности

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АННОТАЦИЯ

Обоснование. Несмотря на доступность визуального исследования шейки матки, цервикальный скрининг в России в должной степени не внедрен, поэтому заболеваемость раком шейки матки остается на стабильно высоком уровне. В последние годы особая роль среди факторов риска возникновения доброкачественных и злокачественных заболеваний шейки матки отведена состоянию цервиковагинальной микробиоты.

Цель исследования — сравнить цервиковагинальную микробиоту у пациенток с плоскоклеточными интраэпителиальными поражениями высокой степени злокачественности (high grade squamous intraepithelial lesions, HSIL) и без предраковых поражений шейки матки (negative for intraepithelial lesion or malignancy, NILM).

Материалы и методы. С помощью метода масс-спектрометрии выполнена идентификация выделенных микроорганизмов из цервиковагинальной микробиоты у 40 пациенток. Из них у 20 женщин выявлена дисплазия шейки матки тяжелой степени и у 20 практически здоровых женщин отсутствовали какие-либо поражения шейки матки.

Результаты. У пациенток с плоскоклеточными интраэпителиальными поражениями высокой степени злокачественности из цервиковагинального микробиома достоверно чаще выявляли бактерии рода *Corynebacterium* spp. и *Streptococcus* spp., чем у женщин без предраковых поражений.

Заключение. Полученные результаты позволяют предполагать, что наличие бактерий рода *Corynebacterium* spp. и *Streptococcus* spp. в цервиковагинальной микробиоте сопряжено с наличием цервикальных интраэпителиальных изменений тяжелой степени злокачественности.

Ключевые слова: дисплазия шейки матки; цервиковагинальная микробиота; HSIL; рак шейки матки.

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The role of cervicovaginal microbiota in the occurrence of severe cervical intraepithelial dysplasia

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ABSTRACT

BACKGROUND: Despite the availability of visual examination of the cervix, cervical screening in Russia has not been widespread enough, and therefore the incidence of cervical cancer remains consistently high. In recent years, the vaginal microbiota is given special attention as a risk factor for the development of precancerous diseases of the cervix.

AIM: The aim of this study was to compare the cervicovaginal microbiota in patients with high-grade squamous intraepithelial lesions (HSIL) or negative for intraepithelial lesions or malignancy (NILM).

MATERIALS AND METHODS: Microorganisms isolated from the cervicovaginal microbiota were identified in 40 patients using the mass spectrometry method. 20 women had severe cervical dysplasia, and the other 20 were healthy women without precancerous cervical lesions.

RESULTS: *Corynebacterium* spp. and *Streptococcus* spp. were found more often in the cervicovaginal microbiome in patients with high-grade squamous intraepithelial lesions than in women negative for intraepithelial lesions or malignancy.

CONCLUSIONS: The data obtained suggest that the presence of *Corynebacterium* spp. and *Streptococcus* spp. in the cervicovaginal microbiota is associated with the presence of severe cervical intraepithelial changes.

Keywords: cervical dysplasia; cervicovaginal microbiota; HSIL; cervical cancer.

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BACKGROUND

According to the World Health Organization, cervical cancer (CC) is the fourth most prevalent cancer among oncological pathologies and constitutes a significant threat to women's reproductive health and life [1, 2]. In 2021, CC was identified in 126.7 observations per 100 thousand population in Russia [3]. The early diagnosis of cervical precancerous lesions is crucial, as it significantly reduces CC incidence [4].

The human papillomavirus (HPV) is the most significant etiologic factor of cervical intraepithelial neoplasia (CIN) and CC [5–7]. In approximately 80%–90% of cases, the papillomavirus infection is spontaneously eliminated. However, in 10%–20% of cases, HPV persists and increases CIN and CC risk [8]. Several contributing factors to the persistence of HPV have been identified, including smoking, HIV infection, autoimmune diseases, age, and cervicovaginal microbiota disruption [9]. Consequently, microbial imbalance affects female reproductive health, susceptibility to infections, and the course of various infections, including sexually transmitted infections, such as HPV [10]. There is increasing evidence on the effect of chronic cervicitis on the course and progression of CIN.

Advances in medical microbiology in the previous years have enabled the assessment of the vaginal microbiota. In 2011, a new classification of vaginal community types was proposed and was supplemented in 2020 [11]. Several studies of the vaginal microbiome are based on this classification, and CIN severity is correlated with an increase in the number of vaginal community types [12]. The vagina is typically populated by bacteria of the genus *Lactobacillus*, which produce an acidic reaction in vaginal fluid. This fluid contains various biologically active substances that protect against infection and overgrowth of pathogens. Numerous studies have demonstrated a correlation between reduced *Lactobacillus* levels and high bacterial diversity and the presence of HPV, CIN, and CC [10, 13].

This study aimed to compare the cervicovaginal microbiota in patients with high-grade squamous intraepithelial lesions (HSIL) to that in patients without cervical precancerous lesions (negative for intraepithelial lesion or malignancy, NILM).

MATERIALS AND METHODS

A prospective study was conducted at the Department of Obstetrics and Gynecology of Samara State Medical University from November 2021 to April 2022. Forty women of reproductive age (18–45 years) were enrolled and divided into two groups. The study group included 20 patients with HSIL, with a mean age of 36 ± 5.7 years, and the control group consisted of 20 women with NILM and abnormal colposcopic findings, with a mean age of 35 ± 6.7 years.

The inclusion criteria were HSIL diagnosed by cytologic examination, presence of high-risk HPV, and signed informed consent to participate in the study.

Conversely, the exclusion criteria included pregnancy, HIV infection, hepatitis B or C, autoimmune disease, use of antibiotics within 15 days prior to specimen collection, sexual intercourse, or menstruation within 48 h prior to specimen collection.

The participants underwent sterile swab collection of native material from the cervical canal for culture on nutrient medium and subsequent culture studies. Extended colposcopy and targeted cervical biopsy were performed under visualization using a portable digital colposcope (patent pending, 2023127147). The biopsy specimens were placed in Ames liquid transport medium and transported to the laboratory for 2 h under isothermal conditions for microbiological examination. Then, electro-radio-surgical high-frequency cervical conization or pinpoint targeted biopsy and cervical scraping were conducted. The obtained material was sent for histological examination.

In the laboratory, the material was sown on an expanded set of dense nutrient media, including 5% blood agar; anaerobic agar; agars for the isolation of Veillonella, clostridia, bifidobacteria, and lactobacilli (all agars produced by HiMedia, India); and universal chromogenic medium (Bio-Rad, USA). The cultures were incubated for 5 days under aerobic and anaerobic conditions. Thereafter, all isolated microorganisms were identified by time-of-flight mass spectrometry with matrix-assisted laser desorption/ionization (Microflex LT, Bruker).

The species and quantitative composition of microbiota in cervical smears and cervical biopsy and association with cervical intraepithelial changes were evaluated.

Statistical analysis was conducted using the StatTech 3.1.8 software. Correlations were evaluated using Pearson's χ^2 criterion, Fisher's exact test, Mann–Whitney *U*-criterion, and Student's *t*-criterion. $P < 0.05$ indicated significant differences.

RESULTS

A microbiological evaluation revealed that *Streptococcus* spp. were 3.7 times more prevalent in women with severe cervical intraepithelial dysplasia than in those without precancerous cervical lesions. The odds differences were significant (95% confidence interval (CI): 1.420–9.470; $p = 0.027$; Fig. 1). The number of streptococci in patients with CIN in the culture and biopsy were similar (95% CI: 0.288–3.476). These results indirectly indicate the role of streptococci in dysplastic processes in the cervix.

The predominant species within the Streptococcus genus was *Streptococcus anginosus*, which constituted most of the streptococcal species within the main group. They are

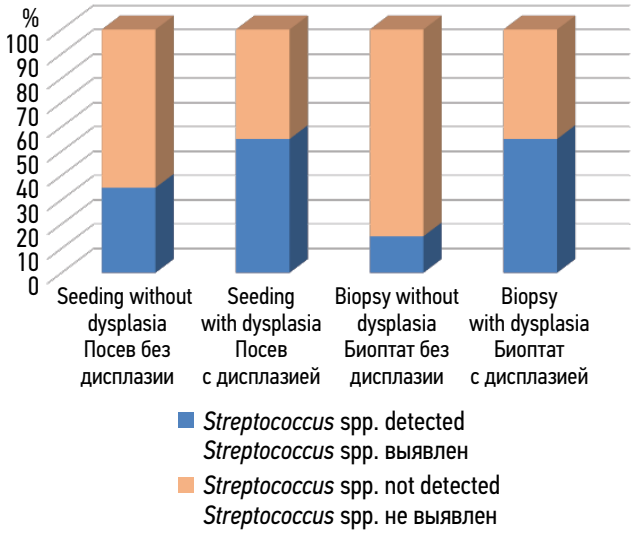

Fig. 1. Presence of *Streptococcus* spp. depending on the presence and absence of cervical dysplasia in culture from the cervical canal and biopsy

Рис. 1. Наличие *Streptococcus* spp. в зависимости от наличия и отсутствия дисплазии шейки матки в посеве из цервикального канала и биоптате

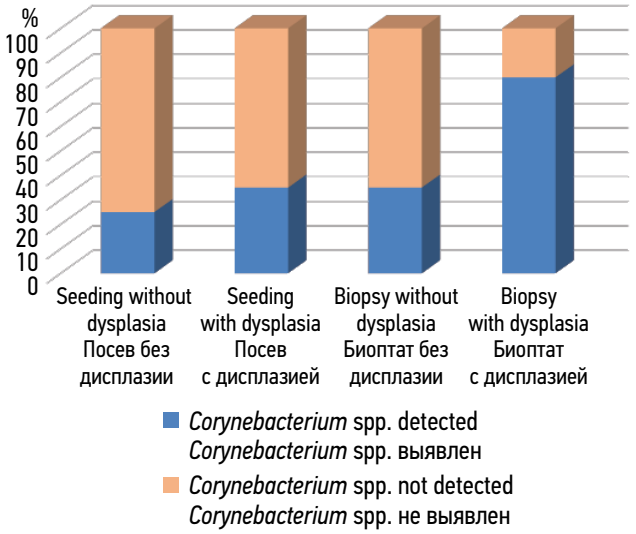

Fig. 2. Presence of *Corynebacterium* spp. depending on the presence and absence of cervical dysplasia in culture from the cervical canal and biopsy

Рис. 2. Наличие *Corynebacterium* spp. в зависимости от наличия и отсутствия дисплазии шейки матки в посеве из цервикального канала и биоптате

part of the oropharyngeal microflora along with *Streptococcus oralis, Streptococcus mitis*, and *Streptococcus sanguinis* and are associated with oral cavity diseases (Table 1). The role of these microorganisms in the development of genital pathology remains poorly understood. The prevalence of unprotected oral–genital contact may be a contributing factor to the occurrence of these bacteria in the vaginal microflora. The results and literature data indicate that the presence of *Streptococcus* spp. is associated with the presence of severe cervical intraepithelial lesions.

Furthermore, significant differences were observed in *Corynebacterium* spp. between the groups. In patients with HSIL, *Corynebacterium* spp. were isolated at a frequency that was 2.8 times higher than that in the comparison group (95% CI: 1.137–7.152; $p = 0.002$; Fig. 2).

These bacteria can adhere to vaginal and cervical epithelial cells, bind to intercellular matrix proteins, and stimulate cytokine production. This allows these bacteria to compete with other microorganisms for adhesion sites and exist in the vaginal microflora in normal and dysbiosis [14]. Data indicate that *Corynebacterium* spp. retains its ability to invade, as 5.6 times more bacteria of this genus were isolated from the cervical biopsy than from the culture. The differences in odds were significant (95% CI: 1.420–21.860; $p = 0.025$). Table 2 presents the species composition of *Corynebacterium* spp.

Table 1. Species composition of *Streptococcus* spp. in the study groups

Таблица 1. Видовой состав *Streptococcus* spp. в группах

***Streptococcus* spp. species**	**Cervical biopsy**		**Cervical canal**	
	Comparison group, *n*	**Study group, *n***	**Comparison group, *n***	**Study group, *n***
S. vestibularis	–	–	1	1
S. oralis	1	3	1	–
S.anginosus	2	8	4	8
S. mitis	–	1	–	1
S. sanguinis	–	1	–	–
S. pseudopneumonia	–	–	–	1
S. galloliticus	–	1	–	–
S.agalactiae	–	1	3	2
S. parasanguinis	–	1	–	–
S. salivarius	–	1	–	–
S. pneumonia	–	1	–	–

Table 2. Species composition of *Corynebacterium* spp. in the study groups
Таблица 2. Видовой состав *Corynebacterium* spp. в группах

Corynebacterium spp. species	Cervical biopsy (number of patients)		Cervical canal (number of patients)	
	Comparison group, *n*	Study group, *n*	Comparison group, *n*	Study group, *n*
C. aurumucosum	4	5	5	6
C. amylocatum	3	5	4	2
C. tuberculostearicum	3	3	1	2
C. simulans	1	2	–	–
C. pyruviciproducens	1	–	–	–
C. mucifaciens	–	1	–	–
C. coyleae	1	1	–	1
C. riegelii	1	–	–	–
C. accolens	–	1	–	–
C. sundsvallense	–	1	–	–
C. minutissimum	–	2	–	–

A statistical analysis (using the Mann–Whitney *U*-criterion) was conducted to compare the patients based on their age of sexual debut. The mean age of sexual debut was 16 (15–18) years in the study group and 18 (17–18) years in the comparison group ($p = 0.010$).

The body mass index of the women was greater in the study group [26 ± 5 (95% CI: 24–29) vs. 23 ± 3 (95% CI: 21–25) kg/m^2 in the comparison group; $p = 0.030$], with an average that was higher than normal.

In the present study, no significant differences were found in smoking rates between the two groups ($p = 0.054$).

DISCUSSION

The results indicate significant differences in cervicovaginal microbiome, age of sexual debut, and body mass index between the groups.

In a study by Chen et al. on patients with HSIL, the *Streptococcaceae* and *Prevotellaceae* families of bacteria were found to be the most prevalent, and the severity of CIN correlated with the number of different types of vaginal communities [13]. Kang et al. revealed the role of Streptococcus in the occurrence of CIN and CC and indicated that the activation of multiple pro-inflammatory cytokines, including interleukin-17, produced in response to streptococcal colonization, affects vaginal and cervical epithelial cells. Moreover, Soares et al. demonstrated that streptococci possess metallopeptidases capable of cleaving extracellular matrix proteins, including fibronectin, laminin, type IV collagen, fibrinogen, and albumin. This process facilitates their penetration into tissues and contributes to bacterial dissemination [15, 16].

The role of corynebacteria in the vaginal microbiome remains unclear. In a study by Manzanares-Leal et al., *Corynebacterium* spp. and *Staphylococcus* spp. were found to be the predominant bacteria in women with CC [17]. In contrast, Gladysheva et al. observed a beneficial effect of *Corynebacterium amycolatum* on the microflora [18]. This underscores the need for further investigation in this field.

The results obtained are comparable with those of other studies in that early initiation of sexual activity is a risk factor for CIN. A meta-analysis of 10 studies involving 6,492 individuals revealed that the earlier women initiated sexual activity, the greater the risk of developing CC [20].

Notably, obesity represents a risk factor for cancer of various localizations. Furthermore, excess body weight has been demonstrated to influence CC progression [22]. Nevertheless, in a case-control study involving 188 women, Ssedyabane et al. found no significant differences in the occurrence of severe dysplasia depending on obesity [23].

A substantial corpus of literature exists on the increased cancer risk associated with smoking. A meta-analysis of 45 studies conducted by Nagelhout et al. showed that smoking plays a role in the development of precancerous lesions and CC [24].

The data on the influence of age on cervical dysplasia onset and progression is inconclusive. Thus, in a study by Zhdan et al. including 120 women (group 1, 40 women with CC; group 2, 80 women without CC), the age of 40 years or above was found to increase the risk of CC by a factor of 14 [25]. Furthermore, in a study involving 314,587 patients, Xiao et al. found no correlation between age and CIN occurrence [26].

CONCLUSIONS

Therefore, the state of the cervicovaginal microflora, age of sexual debut, and body mass index may influence the occurrence of cervical intraepithelial dysplasia of severe

malignancy. The study group exhibited a higher prevalence of *Streptococcus* spp. and *Corynebacterium* spp. in their cervicovaginal microflora, which supports the hypothesis that these species play a role in the development of CIN. No correlation was observed between the other detected microorganisms and cervical intraepithelial changes. The microbiota showed qualitative and quantitative differences between cervical biopsy and cervical smear samples. The occurrence of HSIL was influenced by earlier age of sexual debut and being overweight, whereas smoking induced no effect. The findings underscore the need for further research in this field.

ADDITIONAL INFORMATION

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Author contribution. All the authors have made a significant contribution to the development of the concept, research, and preparation of the article as well as read and approved the final version before its publication.

Personal contribution of the authors: *E.F. Kira* — study concept and design, editing; *A.V. Kazakova, S.M. Chechko* — study concept and design, collection and processing of material, text writing.

Ethics approval. The present study protocol was approved by the local Ethics Committee of the Samara State Medical University (No. 217 dated 10.02.2021).

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