Med Glas (Zenica)

ORIGINAL ARTICLE

Coexistence of aerobic vaginitis caused by Enterococcus faecalis and human papilloma virus (HPV) infection as a risk factor for the development of cervical intraepithelial lesions

Amna Baraković[1], Mahira Jahić[2,3], Anis Cerovac[3-6]*, Fatima Numanović[3]

[1]Primary Health Care Centre "Izudin Mulabećirović Izo", Tešanj, Bosnia and Herzegovina; [2]Gynecological Centre "Dr Mahira Jahić", Tuzla, Bosnia and Herzegovina; [3]School of Medicine, University of Tuzla, Tuzla, Bosnia and Herzegovina; [4]Department of Gynaecology and Obstetrics, General Hospital Tešanj, Bosnia and Herzegovina; [5]Department of Gynaecology and Obstetrics, School for Health Studies, University of Bihać, Bosnia and Herzegovina; [6]Department of Gynaecology and Obstetrics, School of Medicine, University of Zenica, Zenica; Bosnia and Herzegovina

ABSTRACT

Aim To determine the prevalence of aerobic vaginitis (AV) caused by *Enterococcus faecalis (E. faecalis)* in human papilloma virus (HPV)-positive women with pathological Pap test and to determine the most prevalent HPV type associated with *E. faecalis* infection.

Methods This prospective study was conducted at the Gynaecology Centre "Dr. Mahira Jahić" Tuzla and Primary Health Care Centre Tešanj (Bosnia and Herzegovina) in the period between February 2023 and March 2024. The research included 200 women aged 25 to 50 years. The examined group consisted of 100 women with a pathological (examined group) and 100 with a normal (control group) Pap test result.

Results Pathological Pap smears were found in 60 (out of 100; 60 %) women in the examined group: cervical intraepithelial neoplasia (CIN) 1 and CIN 2 in two women, respectively, CIN 3 in seven, atypical squamous cells of undetermined significance (ASCUS) in 29 and atypical squamous cells-high-grade cannot be excluded (ASC-H) in two women. Overall (both groups) prevalence of *E. faecalis* was 25.5% (51women); in 45 (22.5%) women *E. faecalis* was the only bacterial isolate, of which 42 (21%) in the examined group and three (1.5%) in the control group. High-risk HPV types were found in 62 (out of 100; 62%) women with the pathological Pap smear test. The association of *E. faecalis* and high-risk HPV positive women was found in 35 (35%) cases (moderately positive correlation; r=0.198).

Conclusion *E. faecalis* is very common in HPV 16 and 18 positive women and may represent a risk factor in the development of cervical intraepithelial lesions.

Keywords: atypical squamous cells of the cervix, risk factors, Papanicolaou test, uterine cervical dysplasia

INTRODUCTION

Persistent human papillomavirus (HPV) infection is a necessary factor for the development of cervical precancerous lesions and cervical cancer, and the presence of inflammation increases the risk for cancer (1). Changes in the female vaginal microenvironment are closely related to the occurrence and development of cervical cancer (2,3). New evidence suggests that the vaginal microbiota plays an important role in cervical carcinogenesis (4). Vaginal microenvironment is susceptible to microecological imbalance due to infection with pathogenic bacteria (5). Since the cervix is directly exposed to the complex vaginal microenvironment, the risk of cervical lesions increases (6).

Plisko et al. state that the inflammatory processes characteristics of aerobic vaginitis (AV) and HPV-induced cervical dysplastic lesions are crucial for the progression of cervical lesions in invasive cervical cancer (7–9).

Microbial pathogens cause carcinogenesis in a high percentage of about 20% of cancers; for example, hepatocellular carcinoma, Kaposi sarcoma, lymphomas, skin, oropharynx, and respiratory, digestive, and urogenital tracts malignancies (9,10). Specific bacteria or dysbiotic bacteria cause damage to the epithelial barrier, immune dysregulation and genotoxicity and create a tumour-permissive microenvironment (11–13). In recent years, a large number of publications has been released about the association between different vaginal microbiota and cervical intraepithelial neoplasia, suggesting that an abnormal vaginal environment plays an important role in the development of cervical intraepithelial neoplasia (CIN); however, very little is known about the role of gut microbiota in the development of this lesion (5,10,11,14).

Recent studies indicate the presence of HPV 16 genes and genomes in *E. faecalis* in biopsied material of cervical cancer (15,16). HPV 16 genes can be translated and transcribed into these bacteria, and form viral particles in these bacteria that

***Corresponding author:** Anis Cerovac
Phone: +387 32 650 662; fax: +387 32 650 605
E-mail: cerovac.anis@gmail.com
ORCID ID: https://orcid.org/0000-0003-0511-3998

Submitted: 15. Jul. 2024. Revised: 28 Sep. 2024. Accepted: 29 Sep. 2024.

lead to a certain relationship as a risk factor in the progression of cervical lesions towards cancer (9,10,16).

The AV positive for *E. faecalis* is very often unrecognized or ignored and may be the reason for neglected diagnosis (17–19) in that case, in HPV-positive women, there is a justified possibility of long-term infection due to the presence of HPV in *E. faecalis* (20). The presence of HPV in AV positive for *E. faecalis* can lead to persistent HPV infection and the occurrence of high-grade CIN, as well as the progression to cervical cancer (17,18). Severe forms of AV with HPV-induced precancerous lesions of the cervix could have a common and crucial role in the progression of the lesion to invasive cancer (19).

A dominant pathogen in AV, such as *E. faecalis* can reduce the protective effect of lactobacilli by causing inflammation, as well as an increase in IL-6, IL-8 and tumour necrosis factor (TNF), increasing the risk of HPV 16 infection resulting in CIN and cervical cancer (3,17). So far, it is known that the reduction of lactobacilli combined with the diversity of the vaginal microbiota is associated with HPV persistence (3,10,18). HPV infection leads to the loss of lactobacilli, destroying the biological barrier of the local vaginal immune microenvironment and promoting abnormal adhesion of HPV in the vagina. These changes cause local microecological imbalance in the vagina and destroy the local immune functions of the cervix while simultaneously increasing adhesion, invasion and colonization of abnormal microbiota (4,17). This leads to a vicious circle in the vaginal environment and the further development of HPV infection that causes cervical lesions (17).

Whether long-term infection with *E. faecalis* can be a risk factor supporting persistent HPV16 infection is still an open question (12,17). Modulation of the microbiota in terms of intensive treatment of AV could promote the elimination of *E. faecalis* and thereby the removal of HPV and the normalization of lactobacilli, and reverse the nature of HPV infection (11). According to various studies (6,11,12), vaginal microbiota plays a crucial role in the prevention of HPV infection and accelerates HPV clearance.

A coexistence of aerobic vaginitis and HPV infection as a risk factor for the development of cervical intraepithelial lesions is currently under investigation in many studies, but there is still no clear answer to our questions in the literature. The aim of this study was to determine the frequency of AV caused by *E. faecalis* in HPV positive women with pathological Pap test and determine the most frequent HPV type associated with the presence of *E. faecalis* in vaginal flora. The results of the study will encourage further research and will certainly serve gynaecologists in their daily practice with patients.

PATIENTS AND METHODS

Patients and study design

The prospective study was conducted in the Gynaecology Centre "Dr. Mahira Jahić" Tuzla and the Health Centre Tešanj in the period between February 2023 and March 2024. The research included 200 women aged 25 to 50 years. During the examination, two groups of tested women were formed. The examined group included 100 women with abnormal Pap smear findings: atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells with suspected high-grade lesion (ASC-H), cervical intraepithelial lesion (CIN) of mild degree (CIN1), moderate degree (CIN 2), and high-grade cervical intraepithelial lesion (CIN3).

A control group included 100 women with a normal Pap test.

Methods

The data on age, professional status, number and mode of deliveries, number of abortions, and smoking habit were collected through the interviews. During the gynaecological examination, on the basis of the previous colposcopy examination, a cytological swab was taken from the surface of the cervix, endocervix and posterior fornix of the vagina, another swab of the vagina was taken for microbiological analysis for aerobic and anaerobic microorganisms, and in the case of pathological Pap smear, a swab was taken for HPV typing. Swabs for bacteriological examination were sent for microbiological processing to the Polyclinic "Life M" Tuzla and the Health Centre Tešanj. Swabs for HPV typing were taken with a brush from the cervical canal and transported in a test tube to the "Nalaz" laboratory in Tuzla for analysis. The findings were then forwarded by e-mail to the Gynaecology Centre "Dr. Mahira Jahić" and the Tešanj Health Centre. Cytological analysis was performed by two experienced cytologists and included vaginal microbiota analysis (presence of lactobacilli and coccal microbiota) and squamous cell analysis.

Statistical analysis

The obtained results were processed using the methods of descriptive statistics, student's t test and χ^2 test. A difference for a value of $p<0.5$ was considered statistically significant, and a difference of $p<0.01$ was considered statistically highly significant.

RESULTS

The average age of women was 38.5±1.8 (Table 1).

In the examined group 32 (32%) women had high education and pathological Pap test comparing to the control group where 10 (10%) women had high education ($p<0.05$) (Table 1).

The habit of smoking was significantly more frequent in the examined group, 38 (19%), compared to the control group, 24 (12%) ($p<0.05$) (Table 1).

From the total of 100 women in the examined group, 60 (60%) had CIN 1, CIN 2 two (2%), CIN 3 seven (7%), ASCUS 29 (29%) and ASC-H two (2%) women. Benign cellular changes (proper Pap test) was found in all 100 women of the control group.

Microbiological examination showed normal findings in 84 (42%) of all tested women, 20 (10%) in the examined group and 64 (32%) in the control group (Table 2).

E. faecalis was found in 51 (out of 200; 25.5%) women; it was identified as a single isolate in 45 (22.5%) women, of which 42 (21%) in the examined group and three (1.5%) in the control group. *E. faecalis* was associated with *E. coli* in four (2%) cases and in one (0.5%) case with *E.coli* and *Enterobacter* spp in the examined group. *E. faecalis* was found to be associated with *Candida albicans* in one case in the control group (Table 2).

Table 1. Baseline characteristics of the women

Characteristic	Examined group N=100	Control group N=100	p
Mean±SD age(years)	38.1±1.7	39.1±1.9	>0.05
	No (%)		
Marital status Married/single	73 (73) /27 (27)	85 (85) /15 (15)	<0.05
Educational status Secondary school/Faculty	68 (68) /32 (32)	90 (90) /10 (10)	<0.05
Smoking Yes/No	38 (38) /62 (62)	24 (24) /76 (76)	<0.05
Mode of delivery Natural childbirth/cesarean section	96 (96) /4 (4)	87 (87) /13 (13)	>0.05
Average number of births	1.36	1.59	>0.05
Average number of abortions	0.38	0.36	>0.05

Table 2. Microbiological findings in 200 women according to the group

Microbiological finding	No (%) of women in the group		
	Examined	Control	Total
Normal	20 (10)	64 (32)	84 (42)
E. faecalis	42 (21)	3 (1.5)	45 (22.5)
E. coli	25 (12.5)	5 (2.5)	30 (15)
Enterobacter spp.	1 (0.5)	0 (0)	1 (0.5)
Ureaplasma urealyticum	3 (1.5)	1 (0.5)	4 (2)
Candida spp.	3 (1.5)	22 (11)	25 (12.5)
E. coli and *E. faecalis*	4 (2)	0 (0)	4 (2)
E. coli, E. faecalis and *Enterobacter* spp.	1 (0.5)	0 (0)	1 (0.5)
Streptococcus agalactiae	1 (0.5)	0 (0)	1 (0.5)
E.coli and *Candida* spp.	0 (0)	1 (0.5)	1 (0.5)
E. faecalis and *Candida* spp.	0 (0)	1 (0.5)	1 (0.5)
Candida spp. and *Streptococcus agalactiae*	0 (0)	1 (0.5)	1 (0.5)
Proteus mirabilis	0 (0)	2 (2)	2 (1)
Total	100 (50)	100 (50)	200 (100)

High-risk HPV was positive in 62 (62%) women with a pathological Pap smear test.

Both HPV types 16 and 18 were presented in 20 (20%) women of the examined group; HPV type 16 was found in 14 (14%) and HPV 18 in one (1%) case. A moderately positive correlation was found between *E. faecalis* and the HPV status in the examined group (r=0.198) (Table 3).

The analysis of the association between *E. faecalis* and HPV positive women found that HPV 16 type was positive for *E. faecalis* in 14 (14%) cases, HPV 16 and 18 in 10 (10%) cases; in six (6%) cases HPV 16,18, 31, 33, 35 were positive for *E. faecalis* and in five (5%) cases for HPV 31, 33, 35 were positive for *E. faecalis*. Only seven (7%) HPV-negative women were positive for *E. faecalis. E. faecalis* and *E. coli* were most frequently isolated pathogens as a cause of AV in the women with pathological Pap test. The analysis of the association between *E. coli* and HPV positive women found that HPV high risk types were positive for *E. coli* in 8 (8%) cases. Thirteen (13%) HPV-negative women were positive for *E. coli* (Table 4).

DISCUSSION

This study aimed to determine the role of *E. faecalis* in the progression of cervical lesions and the status of HPV infection. Dysbiosis (disturbance of microbiota homeostasis) can threaten health by increasing the host's susceptibility to infections. It has been shown that various factors including life style, age, hygiene, sex, genetics of the host, nutrition, environmental factors, type of delivery, dietary patterns can affect the microbiota (14,21–23). Analysing the professional qualification, it is very interesting that a larger number of women from our study with a higher professional qualification had pathological Pap test results compared to the control group. It can be speculated that better educated women are more often subjected to gynaecological examination compared to less educated women.

Smoking as a risk factor should be highlighted because out of the total number of women in our study 31% consumed cigarettes and women with CIN lesions consumed tobacco significantly more often. Women who use cigarettes are more prone to the appearance of cervical intraepithelial lesion, as well as to developing cervical cancer (24,25).

The oral mucosa and the mucosa of the vagina and cervix have a very similar morphological structure, so pathogens that make changes on those mucous membranes can probably also affect changes in the female genital organs (16,26). A very scarce number of publications about this relationship was found (16).

The frequency of AV varied from 12% to 23.7% in symptomatic women who are not pregnant and 4 to 8% during pregnancy (27). *E. faecalis*is was the most frequently isolated pathogen in AV up to 31% (19,22). In our research, *E. faecalis* was presented in 25.5% of women (as a single pathogen in 22.5% and in 3% associated with other bacteria).

Table 3. HPV status/types of 100 women with abnormal Pap smear finding (examined group)*

HPV status/type	No (%) of women in the examined group
Negative	38 (38)
Positive	62 (62)
16,18	20 (20)
31,33,35	6 (6)
16,45,51,52	1 (1)
16,18,31,33,35	1 (1)
16	14 (14)
33,39	1 (1)
18,59	1 (1)
16,56	1 (1)
31,52	1 (1)
16,31,33	1 (1)
39	2 (2)
31	2 (2)
52,59	3 (3)
39,51,59	1 (1)
18,45,56	1 (1)
31,58	1 (1)
16,45	1 (1)
35,58	1 (1)
33	1 (1)
51,59	1 (1)
16,51	1 (1)
Total	100 (100)

*women with abnormal Pap smear finding: atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells with suspected high-grade lesion (ASC-H), cervical intraepithelial lesion (CIN) of mild degree (CIN1), moderate degree (CIN 2), and high-grade cervical intraepithelial lesion (CIN3)

Table 4. *E. faecalis* and *E. coli* in relation to the HPV status/types of 100 women with pathological Pap test*

Combination of pathogens	Number (%)of women
E. faecalis + HPV 16	14 (14)
E. faecalis + HPV 16,18	10 (10)
E. faecalis + HPV 31	3 (3)
E. faecalis + HPV 31,33,35	2 (2)
E. faecalis + HPV 16,18,31,33,35	6 (6)
E. faecalis + HPV negative	7 (7)
E.coli + HPV 16	2 (2)
E.coli + HPV 16,18	2 (2)
E.coli + HPV 31,33,35	1 (1)
E.coli + HPV 16,18,31,33,35	3 (3)
E.coli + HPV negative	13 (13)

**E. faecalis* and *E. coli* were most frequently isolated pathogens as a cause of aerobic vaginitis in women with pathological Pap test

In our study *E. faecalis* in HPV-positive women was found in 35%. Carillo et al. also found a frequency of *E. faecalis* of 27% in HPV-positive women suggesting a close relationship between cancer and the microbiota identified as the "oncobiome" (28).

A positive correlation between AV and HPV infection was found in some studies but there are also differences between the results of different studies (29).

Persistent human papilloma virus (HPV) infection is a necessary factor for the development of precancerous cervical lesions and cervical cancer (21). The most common type of HPV present in CIN 1 is HPV 16 (26.3%), also HPV 6, 18, 31, 39, 51, 52, 53, 56, 59 are involved (30). The most common type in CIN 3 is also HPV 16 (45.3%). Regardless of the diagnosis, HPV 16 is the most common type of HPV globally, which confirmed our research also (30).

Our results showed 35% *E. faecalis* prevalence in HPV positive women and in 7% in HPV negative women. Most often *E. faecalis* was associated with HPV 16 (14%). The AV is a greater predictor of CIN lesions than bacterial vaginosis (BV) (23,31). The AV has an increased pH of the vaginal environment and a reduced number of lactobacilli, which are key promoters of HPV reproduction in the cervix (17). Evidence suggests that the cervico-vaginal microbiota may be involved in the dynamics of HPV infection (6). Women with a certain composition of the cervicovaginal microbiota may be more susceptible to HPV infection, have no clearance from the infection, or show faster progression to cervical neoplasia (3,6,29).

This is the first study in Bosnia and Herzegovina as far as we know that linked AV caused by *E.faecalis*, HPV and precancerous lesions on the cervix. Some interesting data and conclusions came out from our study: *E. faecalis* was the most common pathogen isolated in examined women with AV, high-risk HPV was positive in 62% women with a pathological Pap smear test, the most common form of pathological pap smear tests were CIN 1 and ASCUS; the analysis of the association between *E. faecalis* and HPV positive women found that HPV was positive in 35% cases of AV caused by *E. faecalis*.

In our study, we found an important difference of *E. Faecalis* prevalence between HPV-positive and HPV-negative women. Our focus was *E. faecalis*, so we did not comment on other pathogens found. Our study examined a connection of *E. faecalis* as a specific cause of AV with HPV infection and high-risk types of HPV and the consequences of their joint action, that is, cytological changes on the cervix, which represent a novelty in the available published studies.

In conclusion *E. faecalis* was very common in HPV positive women with pathological pap test and was most often found in HPV 16 positive women. The association of those two pathogens may represent a risk factor in the development of cervical intraepithelial lesions. Multicentric and prospective studies on a larger sample are necessary to confirm our results and conclusions.

AUTHOR CONTRIBUTIONS

Conceptualization, M.J. and A.B.; methodology, M.J., A.B. and F.N.; validation, A.B., M.J. and F.N.; formal analysis, A.B., M.J. and A.C.; investigation, A.B., M.J. and A.C.; resources, M.J. and F.N.; data curation, A.C.; writing—original draft preparation, A.B., M.J. and A.C.; writing—review and editing, A.C.; visualization, A.C.; supervision, A.C.; project administration, A.B.; funding acquisition, A.B. All authors have read and agreed to the published version of the manuscript.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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