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Correlation between High-Risk Human Papilloma Virus (HR-HPV) infection and vaginal microecological abnormalities

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ABSTRACT

Objective: To study the correlation between High-Risk Human Papillomavirus (HR-HPV) infection and vaginal microecological abnormalities, and to investigate the role of vaginal flora in HR-HPV infection.

Methods: A total of 122 HR-HPV-infected patients with negative cervical cytology, who visited the gynaecology clinic of Beijing Ditan Hospital affiliated with Capital Medical University from June 2023 to June 2024, were set as the HR-HPV (+) group. Meanwhile, 94 HPV-negative and cervical cytology-negative women who were examined during the same period were set as the HR-HPV (-) group. The infection rates of Bacterial Vaginosis (BV), Vulvovaginal Candidiasis (VVC), and Trichomonal Vaginitis (TV) were compared between the two groups.

Results: The BV infection rate in the HR-HPV (+) group (15.57%, 19/122) was higher than that in the HR-HPV (-) group (7.45%, 7/94, x^2= 3.312, p>0.05). The VVC infection rate in the HR-HPV (+) group (10.66%, 13/122) was not statistically significant different from that in the HR-HPV (-) group (8.51%, 8/94, x^2 =0.598, P>0.05). The TV infection rate in the HR-HPV (+) group was 2.46% (3/122), slightly higher than in the HR-HPV (-) group (0/94), but the difference was not statistically significant (p=0.259, p>0.05). Conclusion: BV, VVC, and TV may not be related to HR-HPV infection.

Keywords: human papilloma virus, infection, vaginal microecological, abnormalities, correlation

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INTRODUCTION

Persistent infection with High-Risk Human Papillomavirus (HR-HPV) is the main cause of cervical cancer. The relationship between vaginal microecological abnormalities and HR-HPV infection has gradually gain attention from the public. The vaginal micro-environment is composed of the vaginal microbiota, vaginal anatomical structure, immune defence mechanisms, and endocrine regulatory factors [1]. Majority of healthy premenopausal women, the vaginal microbiota is dominated by lactobacilli, which create a low pH environment by producing lactic acid, hydrogen peroxide, and bacteriocins [2-4]. *Lactobacilli*, with their strong adhesion properties, can tightly adhere to the vaginal epithelium and activate the complement system and local immune response, thereby protecting the vagina from colonization by pathogenic microorganisms [5]. Currently, abnormalities of vaginal micro-environment are considered to be potentially related to the acquisition, reactivation, or delayed clearance of HPV infection, as well as the severity of cervical lesions. This study retrospectively analyzes the data of patients aged 18 years-60 years old who visited the gynecology outpatient clinic of Hospital Ditan in Beijing, Capital Medical University, from June 2023 to June 2024, and underwent both HR-HPV testing and vaginal microecological testing, to investigate the correlation between vaginal microecological abnormalities and HR-HPV infection.

MATERIALS AND METHOD

Data source

Retrospective analysis of clinical data from women aged 18 years-60 years old who visited the gynaecology outpatient clinic of Hospital Ditan in Beijing, Capital Medical University, from June 2023 to June 2024, and underwent HR-HPV testing (using the Aptima HPV and Aptima HPV-GT tests) and vaginal microecological testing (using the Pentaplex enzyme method).

Inclusion criteria

History of sexual activity, no antibiotic use in the past week; no sexual activity, vaginal douching, or medication application within the past 72 hours; not in menstruation, pregnancy, or lactation period; no history of cervical surgery or total hysterectomy; no immune system diseases or history of pelvic radiotherapy or chemotherapy. All participants underwent HPV testing, liquid-based cytology, and vaginal microecological testing.

Evaluation methodologies

HPV DNA testing:

Collect cervical exfoliated cells by rotating the sample brush clockwise five times at the cervix and place them in a preservation solution. PCR-reverse dot blot hybridization is used to detect 15 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82) and 2 low-risk types (HPV6, 11).

Diagnosis of vaginal infectious diseases:

The diagnostic criteria for Bacterial Vaginosis (BV), Vulvovaginal Candidiasis (VVC), and Trichomonal Vaginitis (TV) are referenced from Gynaecology and Obstetrics (9th edition).

Pathogen detection in vaginal secretions:

Using 0.9% sodium chloride solution for wet mount microscopy to observe the presence of trichomonads in the secretions under low magnification. Wet mount and Gram stain methods are used to examine the presence of budding spores or pseudohyphae in the secretions under oil immersion microscopy. BV diagnosis is based on a Nugent score ≥ 7.

Cervical TCT testing:

Cervical exfoliated cell specimens are processed using the Thin Prep®2000 system, and the results are classified according to the 2001 TBS system.

Data analysis

Statistical analysis was performed using SPSS 27.0 software. All data are presented as mean ± standard deviation (mean ± SEM), median and interquartile range [median (Q1, Q3)], or percentage. The x^2 test was used for comparisons of qualitative data between groups, and Fisher's exact test was used when the sample size was small. Quantitative data were analysed for normality. For normally distributed quantitative data, intergroup comparisons were made using the t-test; for non-normally distributed quantitative data, intergroup comparisons were made using non-parametric tests. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 122 patients with HR-HPV infection and negative cervical liquid-based cytology were classified as the HR-HPV (+) group, and 94 HPV-negative and cytology-negative women who were examined during the same period were classified as the HR-HPV (-) group. A normality test was performed on the ages of the 2 groups. The age distribution in the HR-HPV (+) group was non-normal (p=0.004), and the age distribution in the HR-HPV (-) group was also non-normal (p=0.011). A non-parametric test for two independent samples was used for comparison. The age of the HR-HPV (+) group was 39.5 (33.00, 49.25) years (range 20 years-60 years), significantly higher than the HR-HPV (-) group age of 36.50 (30.00, 43.25) years (range 23 years-59 years). The difference in age between the 2 groups was statistically significant (p=0.013, p<0.05).

Correlation between HR-HPV infection and BV, VVC, TV

The BV infection rate in the HR-HPV (+) group was 15.57% (19/122), higher than that in the HR-HPV (-) group (7.45%, 7/94), but the difference was not statistically significant (x^2=0.069, p>0.05). The VVC infection rate in the HR-HPV (+) group was 10.66% (13/122), compared to 8.51% (8/94) in the HR-HPV (-) group, with no statistically significant difference (x^2=0.598, p>0.05). The TV infection rate in the HR-HPV (+) group was 2.46% (3/122), compared to 0% (0/94) in the HR-HPV (-) group, with no statistically significant difference (p=0.259, p>0.05) (Table 1).

Tab. 1. Comparison of the incidence rates of various microecological diseases between HR-HPV (+) group and HR-HPV (-) group

Groups	Number of Cases	BV		VVC		TV	
		Number of Cases	Percentage (%)	Number of Cases	Percentage (%)	Number of Cases	Percentage (%)
HR-HPV (+)	122	19	15.57	13	10.66	6	4.92
HR-HPV (-)	94	7	7.45	8	8.51	0	0
x^2 value	-	3.312		0.278		0	
P-value	-	0.069		0.598		0.259	

HR-HPV, High-Risk Human Papillomavirus, Bacterial Vaginitis (BV), Vulvovaginal Candidiasis (VVC), Trichomonal Vaginitis (TV)

DISCUSSION

Recent studies suggest that vaginal microecological disorders may be associated with the occurrence and development of high-risk HPV infections and cervical lesions. When the vaginal microecosystem is disrupted or abnormal, it can easily cause reproductive tract inflammation. Long-term recurrent reproductive tract inflammation may lead to HPV infection or persistent infection, resulting in cervical cancer development [6-10]. When the number of *Lactobacilli spp.* in the vagina decreases, *Gardnerella spp.* or other anaerobic bacteria can proliferate, leading to BV [6].

There are many studies shown on the relationship between BV and HR-HPV infection. Many studies have shown that in BV patients, decrease in *Lactobacilli spp.* and increase in *Gardnerella spp.* and *Prevotella spp.,* will enhances the risk of HR-HPV infection [11-14]. Liu et al. found that BV is associated with HPV in a study of 4290 patients [15]. However, other study by Castle et al., suggests that BV is not associated with HR-HPV [16]. Our study indicates that the incidence of BV in 122 HR-HPV (+) patients is higher than in HR-HPV (-) patients, but the results show no relationship between BV and HR-HPV infection.

VVC is vulvovaginitis caused by opportunistic pathogenic fungi, producing invasive proteases that increase tissue permeability, leading to the disruption of vaginal and cervical epithelial cells. Several studies suggest that VVC may increase the risk of high-risk HPV infection, and HR-HPV (+) patients with VVC have a much lower HPV clearance rate than those without infection [17-20]. However, some studies show no significant association between VVC and high-risk HPV infection [21, 22]. Yang Jin et

al. conducted a study from patients for one year and found that VVC could increase the risk of HR HPV infection, with the HPV clearance rate in VVC and refractory VVC patients being much lower than in those without infection [23]. Our study shows that the incidence of VVC in 122 HR-HPV (+) patients is higher than in HR-HPV (-) patients, but the results suggest that VVC has no significant relationship to HR-HPV infection.

TV is caused by *Trichomonas vaginalis,* which the bacteria destroy vaginal epithelial cells by consuming intracellular glycogen and inhibiting lactobacilli growth. Thus, it leads to significantly reduce in hydrogen peroxide and lactic acid levels, and raise in vaginal pH [6]. The correlation between TV and high-risk HPV infection remains controversial. Yang Jin et al. found no significant correlation between TV and HR HPV infection in a study of 2960 women [23]. However, Li et al. suggested that trichomonads damage the vaginal and cervical mucosa, increase the susceptibility to HR HPV and promotes persistent infection [24]. Lazenby et al. found that the detection rate of HR HPV was significantly higher in TV-infected patients than in non-TV-infected patients, proving a correlation between TV and HR HPV, with TV-infected patients having a 6.5 times higher rate of HPV-16 infection [25]. Our study shows that the incidence of TV in 122 HR-HPV (+) patients is higher than in HR-HPV (-) patients, but the results found no significant correlation between TV and HR-HPV infection.

CONCLUSION

This study indicates that the incidence rates of BV, VVC, and TV in 122 HR-HPV (+) patients are higher than in HR-HPV (-) patients, but the results suggest that BV, VVC, and TV are not related to HR-HPV infection. This may be due to the small number of cases included, but other studies suggest that differences in disease detection methods could lead to different sensitivities, affecting the outcome of results and correlation studies. Therefore, further research with larger sample sizes and different detection methods is needed to determine the role of BV, VVC, and TV in HPV infection as well as the carcinogenesis of those diseases.

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AUTHORS' CONTRIBUTIONS

- RongXu Li: Data curation, Data analysis, Writing – Original draft.
- FuChuan Wang: Resources, Validation, Writing - Original draft.
- Phei Er Kee: Validation, Writing – Review and editing.
- Kai Bin Liew: Conceptualization, Supervision, Writing – Review and editing.

DECLARATION OF CONFLICT OF INTEREST

The authors have no conflict of interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University (2020-017).

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