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Correlation analysis of vaginal flora and immune function Th1/Th2 imbalance in women with high-risk HPV infections in the female reproductive tract

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Abstract

The purpose of this study was to analyze the correlation between vaginal flora and immune function Type 1 helper T cells/Type 2 helper T cells imbalance in females having HPV infections at high risk within the female reproductive tract. We selected 150 female patients who visited our hospital for reproductive tract inflammation between March 2019 and March 2021. They were divided into high-risk HPV-positive and high-risk HPV-negative groups according to the results of the HPV tests. Vaginal flora composition, density, diversity, and Th1/Th2 immune cell cytokine expression were assessed, and their correlations were analyzed. Compared to the HPV-negative group at high risk, the HPV-positive group at high risk exhibited significantly higher rates of Lactobacillus abnormalities, Chlamydia trachomatis and Mycoplasma urealyticum positivity(P<0.05). However, no statistically significant differences in the rates of Neisseria gonorrhoeae, bacterial vaginosis, mould, and trichomonad positivity were observed in both groups (P>0.05). The high-risk HPV-positive group displayed significantly higher rates of abnormal vaginal flora density and diversity compared to the HPV-negative group at high risk (P < 0.05). Compared to the HPV-negative group at high risk, the HPV-positive group at high risk exhibited significantly lower expression levels of Th1, Th1/Th2, IFN-γ, and IL-2 and higher expression levels of Th2, IL-4, and IL-10(P<0.05). Among patients having HPV infections at high risk, those with abnormal vaginal flora had lower expression levels of Th1, Th1/Th2, IFN-γ, and IL-2 and higher expression levels of Th2, IL-4, and IL-10 compared to those with normal vaginal flora, all of which were statistically significant(P<0.05). Vaginal flora dysbiosis was correlated with Th1/Th2 imbalance (P<0.05). Women with high-risk HPV infections in the female reproductive tract exhibit abnormal vaginal flora and immune function Th1/Th2 imbalance, characterized by a shift from Th1 to Th2. Moreover, there is a close correlation between vaginal flora dysbiosis and immune function Th1/Th2 imbalance.

Keywords: High-risk Human Papillomavirus Infection; Vaginal Flora; Immune Function; Type 1 Helper T cells/Type 2 Helper T cells

1. Introduction

The female reproductive tract is a sophisticated and dynamic microecosystem that undergoes constant modulation under the influence of sex hormones. Within this intricate environment, beneficial bacteria intricately contribute to the maintenance of a balanced ecosystem by secreting an array of bacteriocins and cytokines. These substances play a pivotal role in sustaining the acidic environment within the vagina, fostering a harmonious interplay among vaginal flora, the host, and the external environment. This delicate balance collectively ensures the preservation of vaginal microbial ecological equilibrium [1].

The continuous influence of sex hormones orchestrates a finely tuned orchestra of interactions within the female reproductive tract. The intricate dance of beneficial bacteria involves the secretion of bacteriocins and cytokines, serving not only to maintain an acidic environment within the vagina but also to establish a network of mutual regulation and coordination. This dance is crucial for the preservation of vaginal microbial balance, contributing to the overall health and functionality of the female reproductive tract [1].

However, this delicate equilibrium can be disrupted, and the consequences are far-reaching. A disturbance in the balance of vaginal flora can create a conducive environment for opportunistic pathogens to proliferate, potentially leading to the development of various reproductive tract diseases in women [2]. The intricate interplay between the diverse microorganisms inhabiting the female reproductive tract can be easily perturbed, resulting in a cascade of events that may compromise the overall health of this vital system.

Recent research has shed light on the association between human papillomavirus (HPV) infection in the female reproductive tract and vaginal flora dysbiosis, the host's immune response, and the pathogenicity of the virus [3]. HPV, especially high-risk types, has been implicated in a range of gynecological issues, and understanding the

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intricate relationship between the viral infection and the vaginal microbiota is paramount for a comprehensive understanding of the health implications involved.

The immune response in the female reproductive tract, particularly the balance between Type 1 helper T cells (Th1) and Type 2 helper T cells (Th2), is a critical aspect of maintaining health and defending against infections [4]. Th1 and Th2 cells play pivotal roles in orchestrating immune responses, and an imbalance in their function can have profound implications for the host's ability to combat infections effectively. Therefore, evaluating the correlation between vaginal flora and the Th1/Th2 immune function imbalance in women with high-risk HPV infections within the female reproductive tract becomes a crucial avenue of exploration.

This study aimed to delve into this intricate interplay, shedding light on how the disruption of vaginal flora may contribute to immune imbalances in women with high-risk HPV infections. By providing insights into these relationships, our research endeavors to contribute valuable information for the early management and treatment of high-risk HPV infections within the female reproductive tract, potentially offering avenues for preventive and therapeutic interventions. Understanding these complex interactions is fundamental for advancing our knowledge of gynecological health and fostering improved strategies for women's well-being.

2. Materials and Methods

2.1. Study Subjects

Between March 2019 and March 2021, a cohort of 150 female patients who visited our hospital due to reproductive tract inflammation were enrolled in this study. They were split into two groups based on the HPV test results: the high-risk HPV-positive group with 87 cases and the HPV-negative group at high risk with 63 cases. Inclusion criteria: Non-menopausal females aged 21 or older who were sexually active. The HPV-positive group at high-risk was determined based on cervical HPV typing results, with no history of HPV treatment, no vaginal rinsing, medication, or sexual activity within the past 3 days. Exclusion criteria: Menstruating/pregnant/lactating females; individuals who had taken antibiotics, sex hormones, or immunosuppressive drugs within the last two weeks; those with vaginal prolapse; individuals with a history of uterine surgery; those suffering from severe internal medical conditions; and individuals with mental or communication disorders. This study was carried out with approval from our hospital's ethics committee and with the informed consent of the research participants.

2.2. Sample Collection

Collection of Vaginal Secretions: Vaginal secretion samples were obtained from both groups during non-menstrual periods. A vaginal speculum was gently inserted into the vagina to adequately expose the cervix and vaginal wall. Using a dry, sterile cotton swab, an appropriate amount of vaginal secretion was collected from the vaginal fornix or the upper third of the vaginal wall and set aside.

Collection of Vaginal Lavage Fluid: Vaginal lavage fluid was obtained from both groups during non-menstrual periods. A 5ml sterile 0.9% saline solution was used to thoroughly rinse the cervicovaginal portion and the upper third of the vaginal wall. Then, 4 ml of vaginal lavage fluid was aspirated from the posterior vaginal fornix and set aside for analysis.

2.3. Microecological Analysis of Vaginal Flora

Vaginal secretion samples were obtained to assess changes in the vaginal flora, including the presence of lactobacillus, Chlamydia, Mycoplasma, bacterial vaginosis, Neisseria gonorrhoeae, mould, and trichomonad.

Vaginal secretion samples were smeared on slides, dried, and fixed, followed by Gram staining. Vaginal flora density and diversity were examined using a 10×100 oil immersion microscope.

Vaginal flora density was categorized as follows: Grade I (+): 1-9 bacteria in a field of vision; Grade II (++): 10-99 bacteria in a field of vision; Grade III (+++): ≥100 bacteria in a field of vision; Grade IV (++++): Bacteria forming clusters. While grades I or IV indicated problematic vaginal flora ecology, floral density in grades II to III was regarded as a typical vaginal flora ecology.

Vaginal Flora Diversity: Vaginal flora diversity was categorized as follows: Grade I (+): Able to identify 1-3 different species of bacteria; Grade II (++): Able to identify 4-6 different bacterial species; Grade III (+++): Able to identify 7-9 different bacterial species; Grade IV (++++): Able to identify 10 or more different bacterial species. While Grades I or IV indicated abnormal vaginal flora ecology, flora diversity in grades II-III was considered normal vaginal flora ecology.

2.4. Measurement of Immune Function Th1/Th2-Related Cytokines

The collected vaginal lavage fluid was processed by centrifugation at room temperature, with a centrifugation radius of 5 cm and a speed of 3000 r/min for 5 minutes. The supernatant was retained and stored at -80°C.

The percentages of Th1 and Th2 cells were determined using the FACSCalibur flow cytometer (BD, Franklin Lakes, NJ, USA). The Th1/Th2 ratio was computed, and the levels of Th1-type and Th2-type cytokines were examined using ELISA techniques. Th1-type cytokines encompassed Interleukin-2 (IL-2) and Interferon-gamma (IFN-γ), while Th2-type cytokines included Interleukin-10 (IL-10) and Interleukin-4 (IL-4).

2.5. Statistical Analysis

Statistical analysis was performed utilizing Statistic Package for Social Science (SPSS) 26.0 software (IBM, Armonk, NY, USA). Measurement data were presented as $\overline{x}\pm s$. Group comparisons were performed utilizing independent samples *t*-tests. For count data, frequencies and percentages were used to present the results, and group comparisons were made using the x^2 test. Correlations were examined utilizing Spearman correlation analysis. A *P*-value of less than 0.05 was used to indicate statistical significance.

3. Results

3.1. Comparison of Baseline Data in Both Groups

As depicted in Table 1, no statistically significant difference in age was observed in both groups ($P>0.05$). However, when comparing the two groups with regards to weekly sexual activity frequency, number of abortions,

Table 1. Baseline Data Comparison in Both Groups.

	High-risk HPV-negative group(n=63)	High-risk HPV-positive group(n=87)	t/x^2	*P*
Age(year)	29.97±4.22	30.29±4.15	0.463	0.644
Sexual life≥ times per week	12(19.05)	36(41.38)	8.374	0.004
Number of abortions≥3	11(17.46)	40(45.98)	13.272	0.001
Smoking history	17(26.98)	49(56.32)	12.764	0.001
Family history of HPV infection	10(15.87)	33(37.93)	8.694	0.003

Table 2. Comparison of Vaginal Flora Distribution in Both Groups (n, %).

	High-risk HPV-negative group(n=63)	High-risk HPV-positive group(n=87)	x^2	*P*
Lactobacillius abnormalities	23(36.51)	50(57.47)	6.426	0.011
Chlamydia trachomatis-positive	10(15.87)	29(33.33)	5.790	0.016
Mycoplasma urealyticum-positive	18(28.57)	45(51.72)	8.041	0.005
Neisseria gonorrhoeae-positive	9(14.29)	21(24.14)	2.217	0.137
Bacterial vaginosis-positive	16(25.40)	29(33.33)	1.096	0.295
Mould-positive	11(17.46)	21(24.14)	0.971	0.324
Trichomonad-positive	15(23.81)	26(29.89)	0.679	0.410

smoking history, and family history of HPV infection, statistically significant differences were observed ($P<0.05$), as depicted in Figure 1.

3.2. Comparison of Vaginal Flora Distribution in Both Groups

As shown in Table 2 and Figure 2, the HPV-positive group at high-risk exhibited a significantly higher rate of Lactobacillius abnormalities, Chlamydia trachomatis and Mycoplasma urealyticum positivity compared to the HPV-negative group at high-risk($P<0.05$). However, no statistically significant differences in the rates of bacterial vaginosis, Neisseria gonorrhoeae, mould, and trichomonad positivity was observed in both groups ($P>0.05$).

3.3. Comparison of Vaginal Flora Density and Diversity between Groups

As shown in Table 3 and Figure 3, compared to the HPV-negative group at high-risk, the HPV-positive group at high-risk exhibited a significantly higher rate of abnormal vaginal flora density and diversity($P<0.05$).

3.4. Comparison of Th1/Th2-Related Cytokine Expression between the Two Groups

As shown in Table 4 and Figure 4, the high-risk HPV-positive group showed significantly lower expression levels of Th1, Th1/Th2, IFN-γ, and IL-2, and higher expression levels of Th2, IL-4, and IL-10 as compared to the HPV-negative group at high-risk ($P<0.05$).

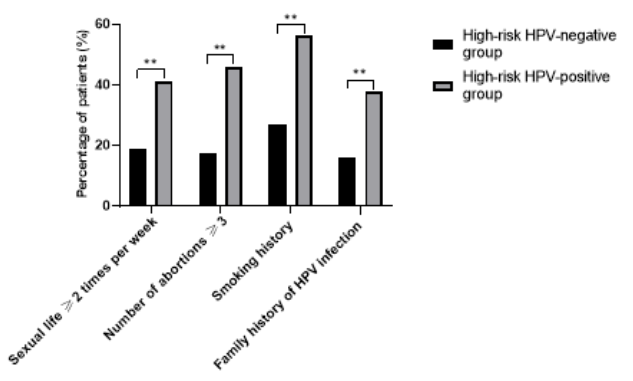

Fig. 1. Comparison of Clinical Data in Both Groups ($^{**}P < 0.01$).

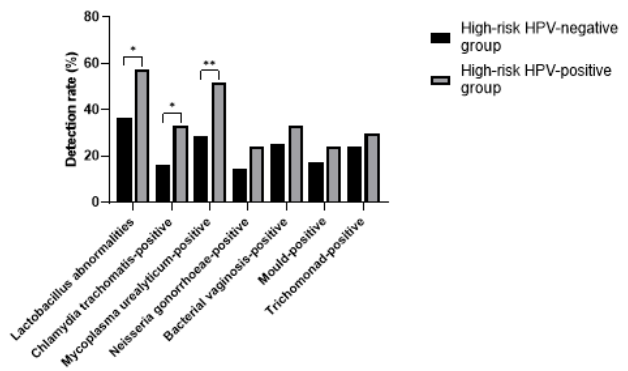

Fig. 2. Comparison of Vaginal Flora Distribution between the Two Groups ($^{*}P<0.05$, $^{**}P<0.01$).

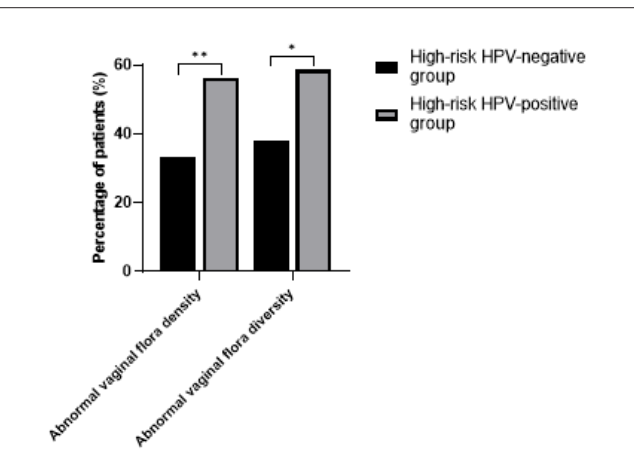

Fig. 3. Comparison of Vaginal Flora Density and Diversity in Both Groups ($^{*}P<0.05$, $^{**}P<0.01$).

3.5. Comparison of Th1/Th2-Related Cytokine Expression between High-Risk HPV-Positive Patients with Normal and Abnormal Vaginal Flora

As shown in Table 5, those with abnormal vaginal flora in the high-risk HPV-positive group exhibited significant-

Table 3. Comparison of Vaginal Flora Density and Diversity in Both Groups (n, %).

		High-risk HPV-negative group(n=63)	High-risk HPV-positive group(n=87)	x^2	*P*
Vaginal flora density	Normal	42(66.67)	38(43.68)	7.759	0.005
	Abnormal	21(33.33)	49(56.32)		
Vaginal flora diversity	Normal	39(61.90)	36(41.38)	6.158	0.013
	Abnormal	24(38.10)	51(58.62)		

Table 4. Comparison of Th1/Th2-Related Cytokine Expression in Both Groups ($\overline{x} \pm s$).

		High-risk HPV-negative group(n=63)	High-risk HPV-positive group(n=87)	*t*	*P*
Th1(%)		22.88±1.89	18.14±2.33	13.286	<0.01
Th2(%)		2.33±0.15	5.77±1.64	16.583	<0.01
Th1/Th2		9.54±0.54	3.54±1.46	31.091	<0.01
Th1-type cytokine	IFN-γ(pg/ml)	26.85±1.27	15.72±2.06	37.958	<0.01
	IL-2(pg/ml)	35.45±2.25	20.60±3.66	28.523	<0.01
Th2-type cytokine	IL-4(pg/ml)	25.55±2.02	34.98±4.47	15.619	<0.01
	IL-10(pg/ml)	15.71±1.22	23.77±3.46	17.696	<0.01

Table 5. Comparison of Th1/Th2-Related Cytokine Expression between High-Risk HPV-Positive Patients with Normal and Abnormal Vaginal Flora ($\overline{x}$±s).

		Vaginal flora density		*t/P*	Vaginal flora diversity		*t/P*
		Normal (n=38)	Abnormal (n=49)		Normal (n=36)	Abnormal (n=51)	
Th1(%)		20.54±1.15	16.28±0.82	20.159/<0.01	20.57±1.17	16.43±1.08	17.077/<0.01
Th2(%)		4.03±0.37	7.12±0.64	26.519/<0.01	4.02±0.38	7.01±0.85	19.734/<0.01
Th1/Th2		5.14±0.51	2.31±0.25	33.973/<0.01	5.16±0.51	2.40±0.54	24.070/<0.01
Th1-type cytokine	IFN-γ(pg/ml)	17.84±1.10	14.08±0.60	20.340/<0.01	17.88±1.11	14.19±0.84	17.702/<0.01
	IL-2(pg/ml)	24.59±1.25	17.50±0.57	35.258/<0.01	24.59±1.26	17.77±1.52	22.090/<0.01
Th2-type cytokine	IL-4(pg/ml)	30.64±1.34	38.33±2.84	15.414/<0.01	30.71±1.35	37.99±3.27	12.604/<0.01
	IL-10(pg/ml)	20.52±1.30	26.30±2.29	13.935/<0.01	20.58±1.30	26.03±2.62	11.507/<0.01

ly lower expression levels of Th1, Th1/Th2, IFN-γ, and IL-2, and significantly higher expression levels of Th2, IL-4, and IL-10 compared to those with normal vaginal flora (P<0.05).

3.6. Correlation Analysis between Vaginal Flora Ecological Changes and Th1/Th2 Immune Function Imbalance

As shown in Table 6, the results of Spearman correlation analysis indicated that changes in vaginal flora ecology were negatively correlated with Th1 and Th1-type cytokines, while positively correlated with Th2 and Th2-type cytokines (P<0.05).

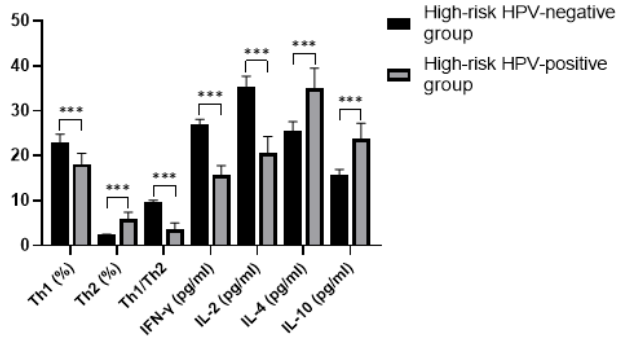

Fig. 14. Comparison of Th1/Th2-Related Cytokine Expression in Both Groups (***P<0.001).

4. Discussion

Under normal conditions, the vaginal flora in women exhibits characteristics of density, diversity, and dynamic balance in microbial proportions. However, when subjected to HPV infection at high-risk, the ecological balance of the vaginal flora is disrupted [5,6]. Studies have found [7] that lactobacillus has inhibitory effects on reproductive system tumors and enhances local immune defenses in the vaginal region. However, when their numbers decrease, it often leads to a decrease in the local immune defense capabilities of the vagina. Pathogens such as Chlamydia trachomatis and Mycoplasma urealyticum can facilitate the replication of high-risk HPV, thereby exacerbating the severity of the infection. In this process, the inflammatory response triggered by the infection not only disrupts the vaginal microenvironment but also damages the local immune barrier in the vagina, increasing the risk of HPV infection-related cervical diseases [8-10]. The results of this study revealed that after HPV infection, there were changes in the dominant bacteria of the vaginal flora, with an increase in Lactobacillus abnormalities, Chlamydia trachomatis and Mycoplasma urealyticum positivity. Addi-

Table 6. Correlation Analysis Between Vaginal Flora Ecological Changes and Th1/Th2 Immune Function Imbalance.

		Th1	Th2	Th1/Th2	IFN-γ	IL-2	IL-4	IL-10
Vaginal flora density	*r*	-0.545	0.528	-0.511	-0.445	-0.513	0.546	0.487
	P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Vaginal flora diversity	*r*	-0.567	0.476	-0.537	-0.498	-0.552	0.558	0.532
	P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

tionally, the local immune defense capability in the cervix decreased. These findings suggest that alterations in the vaginal flora ecology following HPV infection at high-risk can be associated with the imbalance in Th1/Th2 immune function.

Human immune function mainly consists of cellular and humoral immunity. When pathogens invade the body, these two components interact to collectively resist external threats. Research has shown [11-13] that helper T cells contribute to the body's immune response by secreting Th1 and Th2 cytokines, participating in the defense against external invasions. During the immune response process, abnormalities in the expression of Th1 and Th2 cytokines can occur. Specifically, there is a reduction in the secretion of Th1 cytokines, notably IFN-γ and IL-2, along with an elevation in the secretion of Th2 cytokines, particularly IL-4 and IL-10 [14-16]. The findings of this study revealed that compared to HPV-negative at high-risk individuals, those with HPV infection at high-risk had abnormal expression of Th1 and Th2 cytokines in vaginal lavage fluid and a noticeable Th1/Th2 imbalance. These findings suggest that there is an immune response-related Th1/Th2 imbalance in the vaginal environment following high-risk HPV infection.

Under normal circumstances, Th1 cells are the dominant immune response cells when the body is exposed to external viral infections. However, when the virus continues to invade, immune imbalance can occur, and Th2 cells become the dominant immune response cells [17-19]. Within the female reproductive system, when it is invaded by HPV infection, there is a gradual shift in the cellular immune response mediated by Th1, leading to a Th1-to-Th2 shift. This phenomenon is known as immune escape [20,21]. The findings of this study revealed that in individuals with high-risk HPV infection within the female reproductive tract, those with abnormal vaginal flora had decreased expression of IFN-γ and IL-2, along with elevated expression of IL-4 and IL-10. This suggests that while experiencing high-risk HPV infection, there is a close relationship between vaginal flora ecology and Th1/Th2 imbalance. The analysis indicates that these alterations may be attributed to shifts in vaginal flora density, diversity, and predominant bacterial species within the female reproductive tract following high-risk HPV infection. These changes may lead to a Th1-to-Th2 bias in the vaginal immune defense process, ultimately disrupting its homeostasis.

In this study, Spearman correlation analysis was utilized to explore the association between vaginal flora ecology and the Th1/Th2 immune function imbalance. The results showed that changes in vaginal flora ecology exhibited a negative correlation with Th1-type cytokines and a positive correlation with Th2-type cytokines. This further underscores that the disruption of vaginal flora ecology and the Th1/Th2 immune function imbalance occur after high-risk HPV infection within the female reproductive tract.

In summary, female reproductive tract high-risk HPV-infected patients exhibit abnormal vaginal flora ecology and Th1/Th2 immune function imbalance, leading to a shift from Th1 to Th2. Both of these factors play a role in resisting high-risk HPV infection.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study was approved by the ethics committee of The Affiliated Hospital of Inner Mongolia Medical University .

Informed Consent

Signed written informed consents were obtained from the patients.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

JZ designed the study and performed the experiments, RZ collected the data, AA, CD analyzed the data, JZ prepared the manuscript. All authors read and approved the final manuscript.

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