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The Prevalence of HPV and non-HPV STIs Among Iranian Women and Assessment of the HPV/non-HPV STIs Co-infection on Cervical Cell Changes

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ABSTRACT

Background & Objective: Persistent infection with some types of Human papillomavirus (HPV), which are high-risk genotypes, can lead the patients toward cervical cancer and, finally, death. Recent studies showed HPV co-infection with non-HPV sexually transmitted infections (non-HPV STIs) could increase the persistency rate of HPV infections. This study aimed to estimate the prevalence of STIs and assess the association of HPV/non-HPV STIs co-infection on cervical cell changes based on cytological findings.

Materials & Methods: In this cross-sectional study, in addition to the routine cervical screening, including HPV testing and cytological assessment, non-HPV STI testing was performed on 1065 Iranian women. To assess the HPV and non-HPV STIs, commercial kits were used.

Results: 964 (90.5%) women had normal cytology (NILM) results. The overall prevalence of HPV and non-HPV STIs were 39.1% and 68.5%, respectively. HPV-53 (6.5%), -16 (6.1%) and -31 (5.5%) were found as the most prevalent genotypes. Ureaplasma Parvum (UP) (42.7%), Group B Streptococcus (GBS) (23.7%), Candida Species (CS) (23.6%), Ureaplasma Urealyticum (UU) (9.6%), and Mycoplasma Hominis (MH) (7.1%) were found as the most prevalent non-HPV STIs. The co-infection of HPV with GBS played an important role in developing the cervical lesion (P<0.05).

Conclusion: In the present study, the STIs, including HPV, UP, GBS, CS, UU, and MH, were prevalent among the study participant, and it was found that the HPV/GBS co-infection played a significant role in the development of LSIL or worse cytological grades. To clarify this issue, further studies will be conducted.

Keywords: Cervical Lesions, Co-infections, Group B Streptococcus (GBS), Human Papillomavirus (HPV), Sexually Transmitted Infection (STIs)

Introduction

Human papillomavirus (HPV) is one of the foremost common sexually transmitted infections (STIs) around the world **(1)**. Infection with this virus, especially the high-risk (HR) genotypes, could lead to cervical cancer **(2)**. This cancer is considered the fourth most common cancer among women, with 570,000 new cases and 311,000 deaths in 2018 **(3)**. Although vaccination against HPV can dramatically reduce the infection rate and eventually prevent cervical cancer **(4)**, vaccination at the recommended schedule may not occur in developing countries **(5)**.

It is important to note that cervical cancer is multifactorial, and in addition to the persistent HR-HPV infection as the main factor, smoking, using hormonal contraceptives, early sexual activity, the number of sex partners, and chronic inflammation

caused by non-HPV STIs have been highly associated with cervical lesion progression **(6-8)**. The chronic inflammation of the cervix caused by non-HPV STIs could provide conditions to persist the HPV infection, and high-grade cervical lesions may appear in women infected with non-HPV STIs **(9, 10)**. Therefore, investigating STIs prevalence and HPV/non-HPV STIs co-infection to manage non-HPV STIs could be helpful to prevent high-grade cervical lesions.

There is little data in studies regarding this subject in our region. Consequently, we aimed to investigate the prevalence of STIs in our region and assess the HPV co-infection with non-HPV STIs, including Chlamydia trachomatis (CT), Neisseria gonorrhea (NG), Mycoplasma genitalium (MG), Mycoplasma hominis (MH), Ureaplasma urealyticum (UU), Ureaplasma parvum (UP), Candida species (CS), Trichomonas vaginalis (TV), Group B Streptococcus (GBS), Herpes Simplex Virus-1 (HSV-1), HSV-2, Trepanoma pallidum (TP), and Haemophilus ducrei (HD) in two different cytological groups. These groups were women with a cytological result less than LSIL and women with a cytological result of LSIL or worse. We attempted to determine which kind of HPV/non-HPV STIs co-infection can contribute to the incidence of cervical cell changes.

Methods

I **Participants and Study Design**

The study population of this cross-sectional study was over 2000 Iranian women who were visited in private clinics, the Gynecology-oncology Ward of Vali-e-Asr Hospital (Tehran, Iran), and referred to Armin Pathobiology Laboratory (Tehran, Iran) during March 2014-March 2019 for routine screening of cervical cancer, including cervical cell assessment based on liquid samples and HPV genotyping. Among individuals who met the inclusion criteria, 1065 women agreed to participate in this research and provided informed consent. The exclusion criteria were a history of HR-HPV infections/abnormal cytology results, immunological abnormalities/disorders, cervical cancer/precancerous changes, radiotherapy, chemotherapy, hysterectomy, HPV vaccination, smoking, and using hormonal contraceptives. During sampling, none of the individuals were pregnant. The protocol of this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Imam Khomeini Hospital Complex affiliated with Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1397.264).

Sample Collection and Cytological Assessment of the Samples

Cervical specimen collection and cytological assessment of the samples were performed as previously described by Mousavi *et al.* **(11)**. The samples were subjected to simultaneous cytological assessment, HPV DNA genotyping, and the detection of non-HPV STIs. The cytological results were categorized negative for intraepithelial lesion and malignancy (NILM); atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL) and glandular cells abnormalities. The individuals with "unsatisfactory for evaluation" and glandular cell abnormalities were excluded from the co-infection assessment. In order to assess the effect of HPV and non-HPV STI co-infections on the occurrence of cervical lesions, individuals were divided into two groups based on cytological findings. One group with a cytological result less than LSIL (NILM, ASC-US, and ASC-H), and the other group with a cytological results of LSIL and HSIL.

DNA Extraction, HPV, and Non-HPV STIs Detection

The DNA of the samples was extracted using the QIAamp DNA blood mini-kit (Qiagen, Hilden, Germany). The HPV detection and genotyping were performed using the INNO-LiPA® HPV Genotyping Extra-II kit (Fujirebio Europe, Belgium). The latter kit is designed to amplify the L1 region of the HPV genome with biotinylated primers. After amplification, PCR products were subsequently used in reverse hybridization on typing strips to identify HPV genotypes. TENDIGO automation system (Fujirebio Europe, Belgium) was utilized for hybridization steps according to the manufacturer's guidelines. In this study, HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered HR genotypes, while other genotypes were considered low-risk.

The detection of non-HPV STIs, including CT, NG, MG, MH, UU, UP, CS, TV, GBS, HSV-1, HSV-2, TP, and HD was completed by applying the AusDiagnostics STI-16 kit (AusDiagnostics, Australia). Briefly, this kit uses the Multiplex Tandem PCR assay for simultaneous detection of the non-HPV STIs. According to the manufacturer's guideline, this test was carried out using the 24-well easy-plex processor and 384-well high-plex real-time system (AusDiagnostics, Australia).

Statistical Analysis

For the statistical analyses, SPSS software version 23 (SPSS Inc., Chicago, Il., USA) was used. The age of the study participants was presented as mean±SD. The distribution of the HPV positive cases, each HPV genotype/group, and non-HPV STIs were calculated as prevalence. Microsoft Excel 2016 was used to gen erate the graphs. P-value<0.05 was considered statistically significant.

Results

The mean age of the participants was 34.87±8.01 years. Out of 1065 participants, 964 (90.5%) had normal and 84 (7.9%) had abnormal cytology results. The cytological assessment of 17 (1.6%) individuals were not evaluated regarding the "unsatisfactory for evaluation" results. Among the abnormal cytology results, 45 (4.2%), 3 (0.3%), 27 (2.5%), 4 (0.4%), and 5 (0.5%) cases showed ASC-US, ASC-H, LSIL, HSIL, and glandular cell abnormalities, respectively. The widespread STIs, including HPV or non-HPV STIs, were observed in 800 participants (75.12%). We observed that 416 individuals (39.1%) were infected with HPV. Infection with HR genotypes was observed in 293 (27.5%) and LR genotypes in 252 individuals (23.7%). Among the HPV-positive cases, 167 (40.14%) individuals were infected with one, 105 (25.24%) with two, 60 (14.42%) with three, 29 (6.97%) with four, and 34 (8.17%) with five or higher number of HPV genotypes. Twenty-one (5.05%) of the HPV-positive cases were untypable. The prevalence of HPV genotypes among the study participants is summarized in Figure 1. Moreover, 730 (68.5%) cases were infected at least with non-HPV STIs. The prevalence of non-HPV STIs among the study participants is shown in Figure 2.

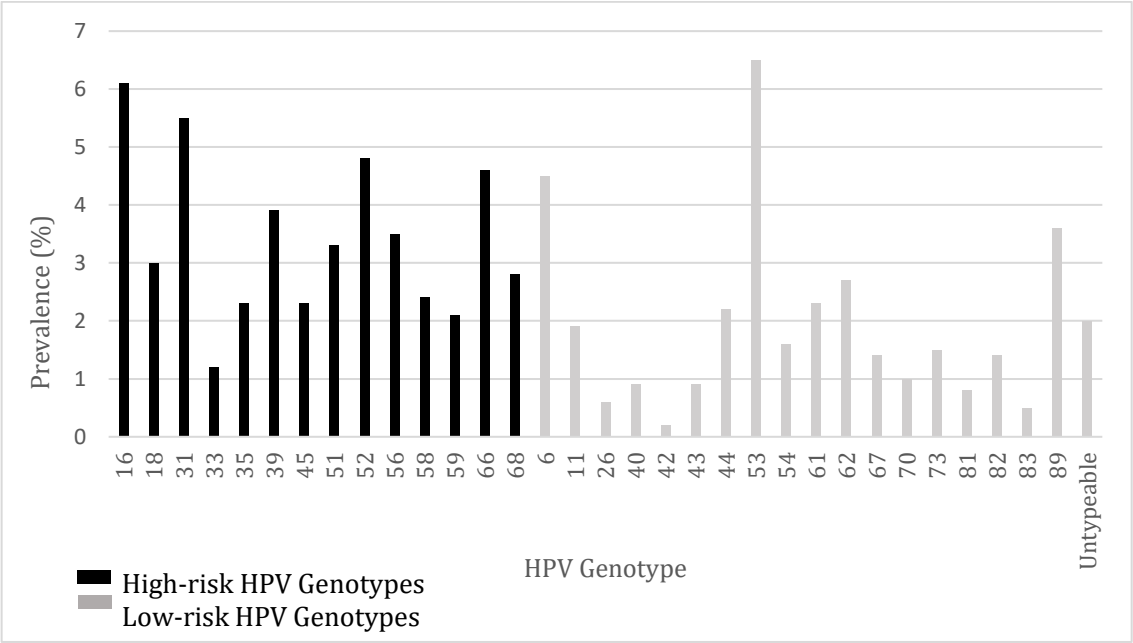

Figure 1. The prevalence of the HPV genotypes among the study participants.

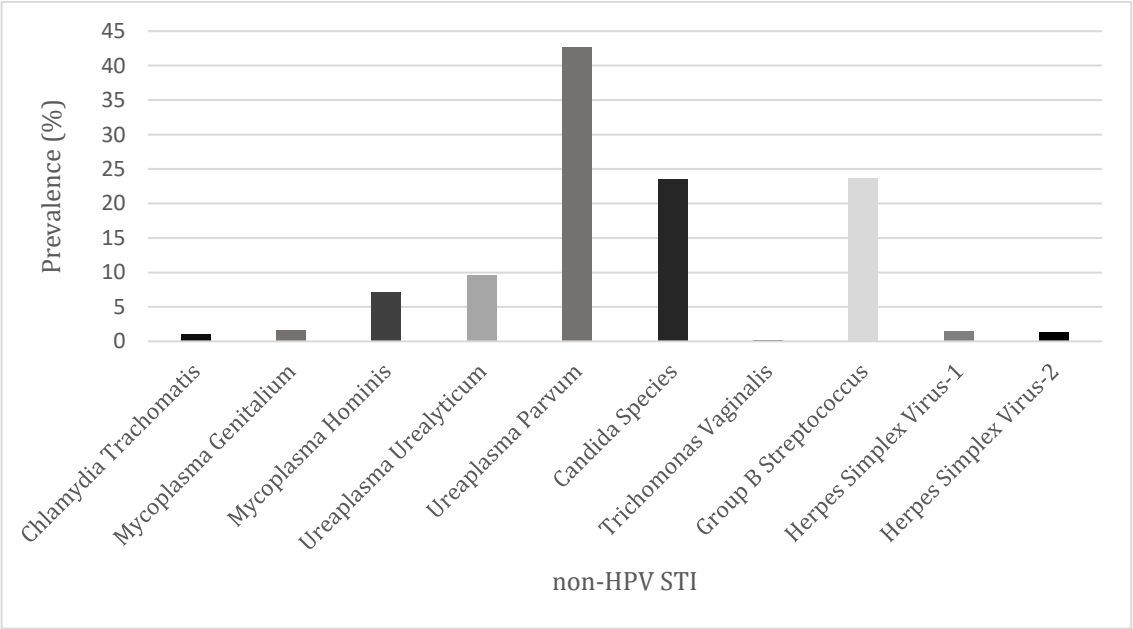

Figure 2. The prevalence of the non-HPV STIs among the study participants

In this study, no infection with NG, TP, and HD was observed. The associations between HPV and non-HPV STIs are presented in Table 1. The associations between the cytological changes and other variables are indicated in Table 2. In this assessment, the "unsatisfactory for evaluation" and glandular cell abnormalities were excluded. Thereafter, variables with statistically significant results ($P<0.05$) were evaluated only in the HPV-positive cases to assess the HPV/non-HPV STI co-infections according to the cytological cut-off (Table 3).

Table 1. The association between HPV and non-HPV STIs

Variables		HPV Positive (n=416)	HPV Negative (n=649)	OR (95%CI)	P-value
Non-HPV STIs	Positive	346 (83.2)	384 (59.2)	3.14 (2.53-4.61)	<0.001*
	Negative	70 (16.8)	265 (40.8)	Ref.	
CT	Positive	8 (1.9)	3 (0.5)	4.22 (1.11-16.00)	0.03*
	Negative	408 (98.1)	646 (99.5)	Ref.	
MG	Positive	14 (3.4)	3 (0.5)	7.50 (2.14-26.26)	0.001*
	Negative	402 (96.6)	646 (99.5)	Ref.	
MH	Positive	49 (11.8)	27 (4.2)	3.08 (1.89-5.01)	<0.001*
	Negative	367 (88.2)	622 (95.8)	Ref.	
UU	Positive	59 (14.2)	43 (6.6)	2.32 (1.54-3.52)	<0.001*
	Negative	357 (85.8)	606 (93.4)	Ref.	
UP	Positive	242 (58.2)	213 (32.8)	2.85 (2.21-3.67)	<0.001
	Negative	174 (41.8)	436 (67.2)	Ref.	
CS	Positive	114 (27.4)	137 (21.1)	1.41 (1.06-1.88)	0.022*
	Negative	302 (72.6)	512 (78.9)	Ref.	
TV	Positive	1 (0.2)	1 (0.2)	1.56 (0.10-25.03)	1.00
	Negative	415 (99.8)	648 (99.8)	Ref.	
GBS	Positive	121 (29.1)	131 (20.2)	1.62 (1.22-2.16)	0.001*
	Negative	295 (70.9)	518 (79.8)	Ref.	
HSV-1	Positive	8 (1.9)	8 (1.2)	1.57 (0.59-4.22)	0.441
	Negative	408 (98.1)	641 (98.8)	Ref.	
HSV-2	Positive	8 (1.9)	7 (1.1)	1.80 (0.65-5.00)	0.291
	Negative	408 (98.1)	642 (98.9)	Ref.	

Table 2. The association between the cytological changes and other variables

Variables		<LSIL (n=1012)	≥LSIL (n=31)	OR (95%CI)	P-value
Age	<30	739 (73.0)	23 (74.2)	1.06 (0.47-2.40)	1.00
	≥30	273 (27.0)	8 (25.8)	Ref.	
HPV	Positive	379 (37.5)	28 (90.3)	15.59 (4.71-51.62)	<0.001*
	Negative	633 (62.5)	3 (9.7)	Ref.	
HR-HPV	Positive	264 (26.1)	21 (67.7)	5.95 (2.77-12.80)	<0.001*
	Negative	748 (73.9)	10 (32.3)	Ref.	
LR-HPV	Positive	227 (22.4)	19 (61.3)	5.48 (2.62-11.45)	<0.001*

Variables		<LSIL (n=1012)	≥LSIL (n=31)	OR (95%CI)	P-value
Non-HPV STIs	Negative	785 (77.6)	12 (38.7)	Ref.	0.009*
	Positive	691 (68.3)	28 (90.3)	4.34 (1.31-14.37)	
CT	Negative	321 (31.7)	3 (9.7)	Ref.	1.00
	Positive	11 (1.1)	0 (0.0)	0.99 (0.98-1.00)	
MG	Negative	1001 (98.9)	31 (100.0)	Ref.	1.00
	Positive	17 (1.7)	0 (0.0)	0.98 (0.98-0.99)	
MH	Negative	995 (98.3)	31 (100.0)	Ref.	0.27
	Positive	71 (7.0)	4 (12.9)	1.96 (0.67-5.77)	
UU	Negative	941 (93.0)	27 (87.1)	Ref.	0.024*
	Positive	94 (9.3)	7 (22.6)	2.85 (1.20-6.79)	
UP	Negative	918 (90.7)	24 (77.4)	Ref.	0.20
	Positive	435 (43.0)	17 (54.8)	1.61 (0.76-3.30)	
CS	Negative	577 (57.0)	14(45.2)	Ref.	0.52
	Positive	237 (23.74)	9 (29.0)	1.34 (0.61-2.95)	
TV	Negative	775 (76.6)	22 (71.0)	Ref.	1.00
	Positive	1 (0.1)	0 (0.0)	1 (1-1)	
GBS	Negative	1011 (99.9)	31 (100.0)	Ref.	0.002*
	Positive	233 (23.0)	15 (48.4)	3.13 (1.53-6.44)	
HSV-1	Negative	779 (77.0)	16 (51.6)	Ref.	0.079
	Positive	14 (1.4)	2 (6.5)	4.92 (1.07-22.63)	
HSV-2	Negative	998 (98.6)	29 (93.5)	Ref.	1.00
	Positive	15 (1.5)	0 (0.0)	0.99 (0.98-0.99)	
	Negative	997 (98.5)	31(100.0)	Ref.	

Table 3. The association between the cytological changes and variables with statistically significant results among the HPV-positive cases

Variables		<LSIL (n=379)	≥LSIL (n=28)	OR (95%CI)	P-value
Non-HPV STIs	Positive	316 (83.4)	26 (92.9)	2.59 (0.60-11.20)	0.28
	Negative	63 (16.6)	2 (7.1)	Ref.	
GBS	Positive	104 (27.4)	14 (50.0)	2.64 (1.22-5.74)	0.016*
	Negative	275 (72.6)	14 (50.0)	Ref.	
UU	Positive	53 (14.0)	5 (17.9)	1.34 (0.49-3.67)	0.58
	Negative	326 (86.0)	23 (82.1)	Ref.	

Discussion

The present study aimed to assess the prevalence of STIs among Iranian women and investigate the associations between HPV/non-HPV STIs co-infection and cytological changes. Normal cytology result was observed in more than 90% of the study participants. The overall prevalence of HPV, HR-HPV, and LR-HPV genotypes was 39.1%, 27.5%, and 23.7%, respectively. It has been reported that more than 290

million people worldwide have been infected with HPV **(12)**, and studies have described diverse HPV prevalence among Iranian women. This difference might result from the limited detection of each HPV assay, detectable HPV genotypes, and the studied groups. The total prevalence of HPV among Iranian women attending regular gynecological checkups was 31.1% by nested-PCR. Moreover, restriction fragment length polymorphism revealed that the most prevalent HPV genotypes were HPV-16 and -18, with a prevalence of 7.3% and 2.8%, respectively **(13)**.

Commercially approved HPV kits, the Geno Array Test kit (Hybribio Limited, Hong Kong) and two versions of INNO-LiPA HPV Genotyping Extra (Fujirebio Europe, Belgium), were applied to detect and genotype HPV in 1387 archival liquid-based cytology and genital lesion samples of women without pre-malignant or malignant cervical disorders, some of whom had genital warts. The results showed that the prevalence of HPV was 40.59% and the most prevalent HPV genotypes were HPV-6 (9.95%), -16 (8.58%), -53 (4.61%), 11 (4.11%) and -31 (4.04%) **(14)**. In the mentioned study **(14)**, some samples had genital warts. Therefore, a higher rate of low-risk genotypes was observed.

In the present research, the most prevalent HPV genotype was HPV-53 (6.5%). According to the literature, this genotype was one of the most common genotypes in Iranian women **(14-16)**. Moreover, in the aforementioned study **(14)**, the authors showed that nearly 70% of individuals were infected with a single HPV genotype. In the current investigation, it was found that only about 40% of the cases were infected with a single genotype. The studied groups and the methods used in the two studies were different. However, the decrease in single genotype infections in our study compared to the mentioned study **(14)** indicates that the prevalence of multiple-HPV genotype infection among Iranian women is increasing, and the HPV infection status of a single genotype is changing to multiple genotype infections.

The most prevalent HR-HPV genotype in the present study was HPV-16 (6.1%), which was consistent with other studies that assessed HR-HPV genotypes. Jamdar *et al.* using the COBAS HPV test (Roche Molecular Systems, Pleasanton CA) reported that the most common HPV genotype in Iranian women was HPV-16 (3%) **(17)**. Moreover, HPV APTIMA assay (Hologic Inc., USA) for detecting HR-HPV E6/E7 mRNA and real-time RT-PCR for the mRNA genotyping of HPV-16,-18, and -45 among Iranian women with normal cytology results showed that the most prevalent HR-HPV genotype was HPV-16 (2.2%) **(18)**. The second most prevalent HR-HPV genotype in the present study was HPV-31 (5.5%), followed by HPV-52 (4.8%) and HPV-66 (4.6%). This pattern of HR-HPV prevalence was also observed in the research by Sohrabi *et al.* (HPV-31: 4%, HPV-52: 3.1%, HPV-66: 2.9%) **(14)**. These findings provide valuable data for developing an HPV vaccine according to the prevalent HPV genotypes in our region.

In addition to assessing HPV prevalence, another main purpose of the present study was to evaluate non-HPV STI prevalence among Iranian women. No comprehensive molecular study about this topic has been conducted yet in our region. The rate of STIs is high, and more than one million new cases are daily diagnosed with either chlamydia, gonorrhea, syphilis or trichomonas's infections **(19)**. It is estimated that over 500 million people are infected with genital HSV-2 **(20)**. We found that the overall prevalence of non-HPV STIs was 68.5%. The most prevalent non-HPV STIs were UP (42.7%), GBS (23.7%), CS (23.6%), UU (9.6%), and MH (7.1%). No infection with NG, TP, and HD was observed. The majority of the previous studies in the other regions demonstrated a lower rate of non-HPV STIs among women. For example, the overall prevalence of STIs in Korean **(21)**, Mexican **(22)**, and Saudi Arabian **(23)** women was 49.2%, 57.7%, and 27%, respectively. However, the studied populations differed from each other. The number of assessed STI pathogens should be considered one of the main reasons that may affect the total prevalence of STIs in each study. According to our and mentioned studies, the most prevalent non-HPV STI was UP **(21, 22)** or Ureaplasma species **(23)**, with a prevalence of 42.7% in the present study and in Korea, 39.8% in Mexico, and 13% in Saudi Arabia. The assessed STI pathogens were not similar in our study and the mentioned investigations. As a result, the second and third most prevalent non-HPV STI pathogens varied. Briefly, the second and third prevalent non-HPV STIs in our study were GBS (23.7%) and Candida species (23.6%), while were MH (9.9%) and UU (7.6%) in Korea, *Gardnerella vaginalis* (25.9%) and CT (1.5%) in Mexico, and Ureaplasma species (21.1%) and MH (4.3%) in Saudi Arabia.

Although several studies showed a significant association between some non-HPV STIs and the presence of HPV, some others revealed no significant association **(23-27)**. For example, Kim *et al.* used real-time PCR to detect seven STI pathogens and multiplex PCR for HR-HPV, and found that non-HPV STI-infected cases had a 1.47 times higher chance of HPV infection. However, no significant association was found when the STI pathogens were assessed separately **(24)**. Displacement amplification for detecting CT and conventional methods for other pathogens showed a significant association between CT or UU and the presence of HPV. In contrast, HPV infection was not significantly correlated with bacterial vaginosis, GBS, CS, TV, and UU **(27)**. In the present study, the overall prevalence of non-HPV STIs among HPV-positive and -negative cases was 83.2% and 59.2%, respectively (OR=3.14, P<0.001). When the non-HPV STI pathogens were evaluated separately, CT, MG, MH, UU, UP, CS, and GBS had a significant association with the presence of HPV, while TV, HSV-1, and HSV-2 did not have a significant association

with HPV presence. It should be noted that the low prevalence of TV, HSV-1, and HSV-2 made it difficult to find statistical significance.

Previous studies found that the co-infection of HPV with some non-HPV STIs could increase the risk of cervical lesions progression. Briefly, de Abreu A. L. *et al.* found that co-infection of HPV with CT, NG, TV, and HSV-2 could raise the risk of ASC-US cytology. Moreover, it was found that HPV co-infection with CT, NG, and TV could augment the risk of HSIL (28). Magalhaes P. A *et al.* reported that CT infection did not increase the risk of HPV infection, while the CT/HPV co-infection could elevate the risk of LSIL development **(29)**. It has also been found that HPV/Ureaplasma co-infection could increase the risk of developing low-grade and high-grade cytological findings **(30-32)**. We assessed all variables that could independently affect cytological changes in all participants and found that in addition to HPV infection as the main factor for cervical cell changes, non-HPV STIs, UU, and GBS could influence the cytological changes. To clarify which of these identified non-HPV STIs may have synergistic interaction with HPV on the dysplastic transformation of cervical cells, these factors were evaluated in HPV-positive cases, and it was observed that HPV/GBS co-infection plays a significant role in the development of the cervical lesion. In other words, 50% of individuals with LSIL or worse cytological grades were infected with GBS. However, only 27.4% of individuals with the lower cytological result than LSIL were infected with GBS. This difference was statistically significant (P=0.016) and showed a greater chance of LSIL or worse cytological progression in the individuals infected with HPV and GBS at the same time. It was revealed that HPV/UU and HPV/non-HPV STIs had no significant association with the development of cervical lesions (Table 3). In the past, assessment of GBS as a non-HPV STI was less critical compared to other non-HPV STIs, such as CT, NG, TV, UU, UP, MG, and MH, and almost none of the research performed on the subject of our study have evaluated this bacteria as a non-HPV STI. Recently, a study used Illumina sequencing-based on 16S rRNA to determine cervical microbiota and suggested that HPV/GBS co-infection could increase the risk of cervical intraepithelial lesion progression **(33)**. Our data confirmed this suggestion, and it was found that the co-infection of HPV with GBS could play a significant role in developing LSIL or, worse cytological grades.

Although this study updated the prevalence of HPV genotypes, revealed good information on non-HPV STIs prevalence, and assessed the association of HPV/non-HPV STIs co-infection in the cytological results of Iranian women, it had some limitations. We evaluated individuals who were referred for routine cervical cancer screening, the number of high-grade cytological results was low, and we were not able to assess the co-infection of HPV with non-HPV STIs in distinct cytological grades. Furthermore, the histopathological data of the participants were not available to investigate the association of HPV/non-HPV STI co-infections with histological changes. Further studies on cervical biopsies are highly recommended.

Conclusion

In conclusion, the sexually transmitted infections including HPV, UP, GBS, CS, UU, and MH were prevalent among the Iranian women participating in this study, and significant correlation between CT, MG, MH, UU, UP, CS, and GBS, and the presence of HPV was observed. Moreover, HPV/GBS co-infection could play a significant role in developing LSIL or, worse cytological grades, which needs further elucidation. Management of GBS infection among the HPV-positive cases is highly recommended.

Acknowledgments

None.

Conflict of Interest

The authors declared no conflict of interest.

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