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Original Article

Prevalence of Sexually Transmitted Pathogen Coinfections in High Risk-Human Papillomaviruses Infected Women in Busan

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High risk-human papillomavirus (HR-HPV) is known to be a major cause of cervical cancer, and coinfection of sexually transmitted pathogen (STP) has been reported to cause persistent HPV infection. However, the relationship between HPV and STP coinfection remains unclear. The purpose of this study was to analyze the coinfection rate with STP in high-risk human papillomavirus infected women in Busan and to collect basic data for the prevention of cervical lesions. This study was carried out in 355 women who had concurrent HPV and STP screening at Busan local hospital between January 2016 and December 2017. HPV and STP coinfection was found in 187 (52.7%) out of 355 cases. HR-HPV and STP coinfection was 82.9% higher than LR-HPV and STP coinfections 17.1%. In HR-HPV infection, *Ureaplasma* species was the most common pathogen (47.1%), followed by *C. trachomatis* (21.9%) and *Mycoplasma* species (12.3%). In the analysis of HR-HPV genotype according to STP, HPV 16 (12.0%) was the most frequent, followed by HPV 58 (11.6%), HPV 39 (11.1%) and HPV 52 (10.2%), but HPV 18 showed a low coinfection rate of 1.3%. According to the results of age, HR-HPV and STP coinfection rate was the highest at 41.9% among women aged 18 to 29. HR-HPV and *Ureaplasma* species showed the highest coinfection rates at all ages, followed by *C. trachomatis* and *Mycoplasma* species. Further studies with more samples will be needed to determine if the coinfection of HR-HPV and STPs is involved in the development of cervical tumors through histologic changes.

Key Words: High Risk-Human Papillomavirus (HR-HPV), Sexually Transmitted Pathogen (STP), Coinfection

INTRODUCTION

Human papillomavirus (HPV) types are classified as high risk groups or low risk groups based on their association with carcinogenic potential and cervical cancer. HPV-related carcinogenesis depends on different factors such as high risk-human papillomavirus (HR-HPV) infection, virus persistence, sustained viral oncogene expression, viral load and viral genome integration (zur Hausen, 2009). In addition to identifying HPV as the main etiological agent, additional risk factors such as use of oral contraceptives, smoking, early onset of sexual activity, multiple partners and chronic inflammation due to coinfection with other microorganisms, have been strongly associated with cervical lesion progression (Castellsagué et al., 2002). Recently, HPV and sexually transmitted pathogen (STP) coinfection have been reported as another cause of persistent HPV infection related to cer-

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vical intraepithelial neoplasia. In particular, *Chlamydia* spp., *Ureaplasma* spp., *Mycoplasma* spp., and HPV coinfection have been reported to be associated with the development of cervical tumors (Bellaminutti et al., 2014; Camporiondo et al., 2016; Zhang et al., 2017; Kim et al., 2018). Although the mechanisms of HPV and STP coinfection in cervical carcinogenesis have not been elucidated yet, several studies have reported high rates of co-infection of HPV with *C. trachomatis*, *M. hominis*, and *U. urealyticum* (Markowska et al., 2002; Camporiondo et al., 2016; Liu et al., 2016). Therefore, it is time to continuously observe how HPV and STP coinfection causes changes in cervical epithelium.

Sex-mediated infection is highly prevalent in sexually active women and is presumed to be associated with HPV infection, as it targets ciliated epithelial cells or transitional epithelial cells. It is known that high rates of STPs in women with HPV infection are due to HPV-related factors such as changes in the immune system of the host or promotion of STPs due to inflammatory reactions (Liu et al., 2016; Zhang et al., 2017). Other studies, STPs have been reported as a modulator of continued development of HR-HPV infection (Silins et al., 2005; Samoff et al., 2005). However, the pathogenesis of HPV and STP coinfection in cervical neoplasia has not been elucidated, there is a lack of research data on HPV and STP coinfection in Korea. Recently the incidence of STPs infection and the prevalence of HR-HPV are increasing at the same time, so early detection and prevention of HR-HPV and STP coinfection may be a way to lower the incidence of cervical neoplasia. Therefore, the purpose of this study was to analyze the coinfection rate with STP in high-risk human papillomavirus infected women in Busan and to collect basic data for the prevention of cervical lesions.

MATERIALS AND METHODS

Study population

This study was performed from January 2016 to December 2017. The results of HPV and STP tests which were performed simultaneously, on 355 women who visited the local hospital in Busan, were analyzed. The age of the 355 women ranged from 18 to 85 years. Ethical approval was obtained from the Institutional Ethics Committee of the Catholic University of Pusan (CUPIRB 2018-01-004). Cervical samples were collected using a cervical swab in 2 mL of phosphate buffered saline (PBS) (Noble Bio, Hwaseoug, South Korea) for detection of HPV and STPs.

Genomic DNA extraction

Genomic DNA extraction was performed from the cervical swab samples by using the QIAamp DNA kit (QIAGEN Inc., Chatsworth, CA, USA) according to the manufacturer's instructions. In brief, 20 μL of proteinase K solution was added to each 1.5 mL tube. And then, 200 μL of sample and 200 μL of AL buffer were added to each tube and briefly vortexed. Each tube was then incubated at 56℃ for 10 min. These were quickly spun down and 200 μL of EtOH was added and briefly vortexed. Again, they were briefly spun down, and total lysate was transferred to a QIAamp MinElute column (Qiagen) and centrifuged at 6,000 ×g for 1 min. Flow through was removed, and 500 μL of AW1 buffer was added and centrifuged at 6,000 ×g for 1 min. After being centrifuged, the flow through was removed and 500 μL of AW2 buffer was added. Then, the samples were centrifuged at 6,000 ×g for 1 min. To dry the column membrane completely, the columns were centrifuged at 20,000 ×g. Each column was then transferred to a new tube, and finally, 30 μL of AE buffer was added to extract gDNA. The columns were incubated at room temperature for 1 min and then centrifuged at 6,000 ×g for 1 min.

Detection of Human papillomavirus genotypes

HPV genotyping was performed by the Omniplex-HPV test (GeneMatrix Inc., Seongnam, Korea) that simultaneously analyzes 40 HPV genotypes (15 HR-HPV types including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82 and 4 probable HR-HPV types including HPV 26, 53, 66 and 69 as well as 21 LR-HPV types including HPV 6, 11, 30, 32, 40, 42, 43, 44, 54, 55, 61, 62, 67, 70, 71, 72, 74, 81, 83, 84 and 87) using the liquid bead microarray (LBMA) method and polymerase chain reaction (PCR) followed by Luminex MAP® technology in HPV DNA extracted from cervical swab samples. Omniplex-HPV testing (GeneMatrix Inc.) was performed according to the manufacturer's instructions. Briefly, Omniplex-HPV uses HPV-specific oligo-

nucleotides for multiplex PCR with a sample quality control targeting the β-globin gene. HPV L1 genes were amplified by using a single-closed tube nested-PCR. Two denaturation steps (2 min at 50℃ and 15 min at 95℃) are followed by 60 cycles of an amplification step; 10 cycles of a pre-amplification step (30 sec for denaturation at 95℃, 30 sec for annealing at 55℃, 60 sec for elongation at 72℃) and 50 cycles of the amplification step (30 sec for denaturation at 95℃, 60 sec for annealing at 40℃, 30 sec for elongation at 72℃) as well as a final elongation step of 10 min at 72℃. Hybridization of amplified PCR products and beads immobilized with probes specific for each of the 40 HPV genotypes was then performed. A polystyrene magnetic bead with a diameter of 6.5 micrometers was internally dyed with various ratios of two spectrally distinct fluorophores to detect various kinds types of genotypes. After hybridization, beads are individually identified using a specialized device within the MAGPIX® system (Luminex Corp., Austin, TX, USA). If the value of MFI (Mean Fluorescence Intensity) is 100 or more, test results are judged to be positive.

Detection of sexually transmitted pathogens

The uterine cervical specimens were examined by using the ISD STD 12 AES TYPING KIT (DIOGENE Co. Seongnam, South Korea) that identify the 12 species of causative organism including (*T. pallidum*, *M. genitalium*, *Neisseria gonorrhoeae*, *U. pavum*, *M. hominis*, *U. urealyticum*, *Gardenerella vaginalis*, *C. trachomatis*, *Trichomonas vaginalis*, HSV I, HSV II, and *Candida albicans*). Cell collection for gDNA extraction requires taking 0.5 mL of specimen and transferring it to a 1.5 mL tube and centrifuging at 1,000 ×g for 5 min. For gDNA extraction, the supernatant is removed completely. 150 μL was added to loosen the cell pellet and samples were boiled for 10 mins at 105℃ on a heat block. After incubation at room temperature, the samples were centrifuged at 12,500 ×g for 5 min. The supernatants were transferred to a new 1.5 mL tube. After PCR reaction, the PCR products were electrophoresed to identify the target specific bands. At this time, when at least one expression occurs in each band, regardless of the STD type, whether positive or negative, the value of the internal control test should be at least 2.0 ng/mL.

RESULTS

Prevalence of coinfection with HPV and STPs

Among 355 cases, HPV and STP coinfection constituted 187 cases (52.7%), which was higher than the 167 cases (47.3%) that were STP negative while being positive for HPV. HPV and STP coinfections were higher in the HR-HPV group (155/187, 82.9%) than in the LR-HPV group (32/187, 17.1%). According to frequency, coinfection of HR-HPV and STPs occurred in the following order: *Ureaplasma* spp. (73/155, 47.1%), *C. trachomatis* (34/155, 21.9%), *Mycoplasma* spp. (19/155, 12.3%), *G. vaginalis* (17/155, 11.0%), HSV II (5/155, 3.2%), *T. vaginalis* (3/155, 1.9%), *N. gonorrhoeae* (2/155, 1.3%) and *Candida albicans* (2/155, 1.3%)

Table 1. Prevalence of coinfection with HPV and STP

Coinfections	Total N=355 (%)	HR-HPV N=155 (%)	LR-HPV N=32 (%)
HPV (+) / STP (−)	168 (47.3)	–	–
HPV (+) / STP (+)	187 (52.7)		
Chlamydia trachomatis		34 (21.9)	3 (9.4)
Ureaplasma urealyticum		60 (38.7)	8 (25.0)
Ureaplasma pavum		13 (8.4)	6 (18.8)
Mycoplasma genitalium		9 (5.8)	–
Mycoplasma hominis		10 (6.5)	4 (12.5)
Gardenerella vaginalis		17 (11.0)	8 (25.0)
Neisseria gonorrhoeae		2 (1.3)	–
Treponema pallidum		–	–
Trichonomas vaginalis		3 (1.9)	–
Herpes simplex virus I		–	1 (3.1)
Herpes simplex virus II		5 (3.2)	1 (3.1)
Candida albicans		2 (1.3)	1 (3.1)

(Table 1).

Coinfection rates with STPs according to HR-HPV genotypes

HPV genotypes were analyzed for a total of 225 cases, including single and multiple infections. In the analysis of coinfection rates with STPs according to HR-HPV genotypes, HPV 16 (27/225, 12.0%) was the most frequent, followed by HPV 58 (26/225, 11.6%), HPV 39 (25/225, 11.1%), HPV 52 (23/225, 10.2%), HPV 53 (22/225, 9.8%) HPV 59 (18/225, 8.0%), HPV 56 (16/225, 7.1%), HPV 51 (15/225, 6.7%), HPV 68 (14/225, 6.2%), and HPV 66 (11/225, 4.9%), but HPV 18 showed a low coinfection rate of 1.3% (3/225) (Table 2).

Among the 27 cases of HPV type 16 infection, 11 cases (40.7%) were co-infected with *Ureaplasma* spp., followed by 7 cases (25.9%) with *C. trachomatis*, and 4 cases (14.8%) with *G. vaginalis* coinfection. HPV 58, 39, 52 and 53 were the most common coinfection of *Ureaplasma* spp., followed by *C. trachomatis* and *Mycoplasma* species (Table 2, Fig. 1).

Positive rate of HR-HPV and STPs coinfection by age group

Comparing coinfection of HPV and STPs according to age, the rate was found to be the highest among those 18 to 29 years of age (65/155, 41.9%), followed by 30 to 39 years (49/155, 31.6%), 40 to 49 years (26/155, 16.8%), 50 to 59 years (15/155, 9.7%). So, coinfection rates of HPV and STP have decreased with age (Table 3). HR-HPV and *Ureaplasma* species showed the highest coinfection rates at all

Table 2. Prevalence of coinfection with STP according to HR-HPV genotypes

Genotypes	Coinfection N (%)	STPs											
		CT	UU	UP	MG	MH	GV	NG	TP	TV	HSV I	HSV II	Candida
HR-HPV 16	27 (12.0)	7	10	1	−	3	4	1	−	−	−	1	−
18	3 (1.3)	1	1	−	−	−	−	−	−	−	−	1	−
26	−	−	−	−	−	−	−	−	−	−	−	−	−
31	5 (2.2)	1	4	−	−	−	−	−	−	−	−	−	−
33	3 (1.3)	1	2	−	−	−	−	−	−	−	−	−	−
35	5 (2.2)	2	2	−	−	−	1	−	−	−	−	−	−
39	25 (11.1)	9	9	1	1	2	2	−	−	1	−	−	−
45	2 (0.9)	1	1	−	−	−	−	−	−	−	−	−	−
51	15 (6.7)	6	5	1	1	1	1	−	−	−	−	−	−
52	23 (10.2)	6	8	3	1	2	2	−	−	−	−	1	−
53	22 (9.8)	4	7	2	3	2	2	−	−	1	−	−	1
56	16 (7.1)	3	6	−	1	3	1	1	−	1	−	−	−
58	26 (11.6)	5	12	3	4	−	2	−	−	−	−	−	−
59	18 (8.0)	3	4	2	2	1	3	−	−	1	−	1	1
66	11 (4.9)	2	4	1	1	1	1	−	−	−	−	−	1
68	14 (6.2)	1	2	2	1	2	3	1	−	1	−	1	−
69	−	−	−	−	−	−	−	−	−	−	−	−	−
70	9 (4.0)	−	9	−	−	−	−	−	−	−	−	−	−
73	−	−	−	−	−	−	−	−	−	−	−	−	−
82	1 (0.4)	−	−	1	−	−	−	−	−	−	−	−	−
Total	225 (100)	52	86	17	15	17	22	3	0	5	0	5	3

CT: *Chlamydia trachomatis*, UU: *Ureaplasma urealyticum*, UP: *Ureaplama pavum*, MG: *Mycoplasma genitalium*, MH: *Mycoplasma hominis*, GV: *Gardenerella vaginalis*, NG; *Neisseria gonorrhoeae*, TP: *Treponema pallidum*, TV: *Trichonomas vaginalis*, HSV I: Herpes simplex virus I, HSV II: Herpes simplex virus II, Candida: *Candida albicans*, STP: Sexually transmitted pathogen

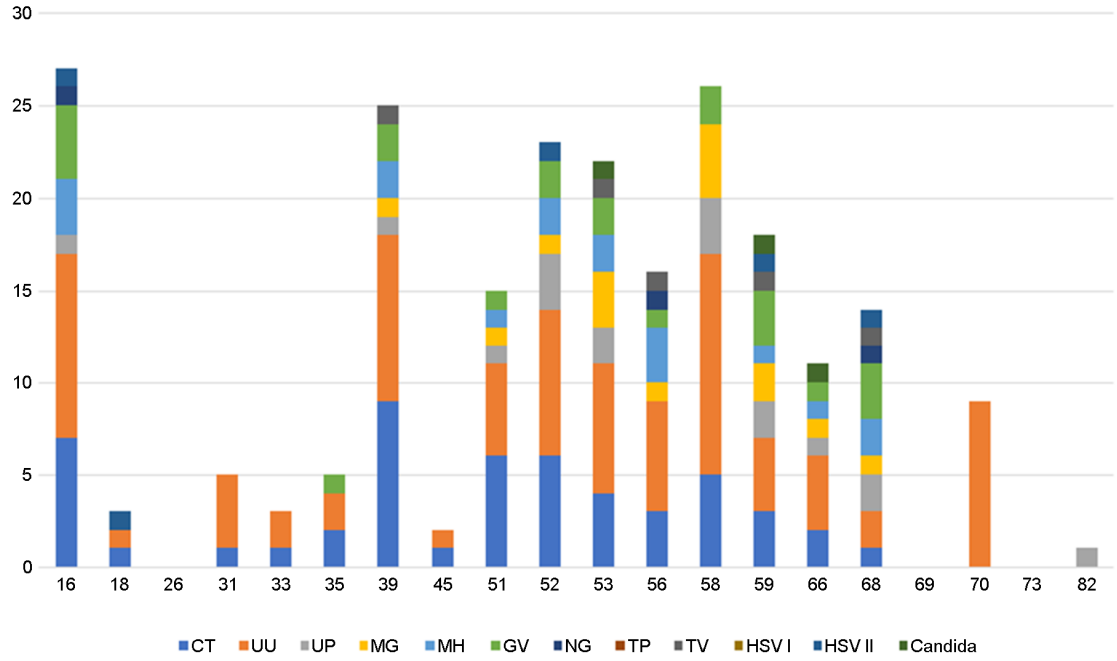

Fig. 1. Distribution of STPs according to HR-HPV genotypes; Among the 27 cases of HPV type 16 infection, 11 cases (40.7%) were coinfected with *Ureaplasma* spp., followed by 7 cases (25.9%) with *C. trachomatis*, and 4 cases (14.8%) with *G. vaginalis* coinfection. HPV 58, 39, 52 and 53 were the most common coinfection of *Ureaplasma* spp., followed by *C. trachomatis* and *Mycoplasma* spp.

Table 3. Positive rate of HR-HPV and STP coinfection by age group

STP	Total N=155	HR-HPV			
		18~29 y N=65	30~39 y N=49	40~49 y N=26	50~59 y N=15
CT	34	16	13	2	3
UU	60	20	23	12	5
UP	13	5	2	5	1
MG	9	4	4	1	−
MH	10	5	2	−	3
GV	17	8	3	4	2
NG	2	1	−	−	1
TP	0	−	−	−	−
TV	3	1	1	1	−
HSV I	0	−	−	−	−
HSV II	5	3	1	1	−
Candida	2	2	−	−	−

CT: *Chlamydia trachomatis*, UU: *Ureaplasma urealyticum*, UP: *Ureaplasma pavum*, MG: *Mycoplasma genitalium*, MH: *Mycoplasma hominis*, GV: *Gardenerella vaginalis*, NG; *Neisseria gonorrhoeae*, TP: *Treponema pallidum*, TV: *Trichonomas vaginalis*, HSV I: Herpes simplex virus 1, HSV II: Herpes simplex virus 2, Candida: *Candida albicans*

ages, followed by *C. trachomatis* and *Mycoplasma* species (Fig. 2).

DISCUSSION

STPs are an important cause of morbidity among sexually active women. HPV infection is one of the most prevalent STPs among women aged under 35 years worldwide (Parthenis et al., 2018), and is a major cause of cervical cancer. The development of cervical lesions depends on infection by HR-HPV genotypes, such as HPV 16 and HPV 18. Persistent HR-HPV infection has been causally associated with cervical intraepithelial neoplasia/squamous intraepithelial lesions (CIN/SIL) and invasive cervical carcinomas (zur Hausen, 2002). Although these HR-HPV infections are naturally overcome by 90% of patients within 1 to 2 years, women with persistent infection have a 100-fold greater chance of developing cervical dysplasia, a pre-cervical cancer stage, than normal women. HR-HPV overexpresses E6 and E7 viral oncogenes and inhibits tumor suppressor genes p53 and pRb, causing transient proliferation of abnor-

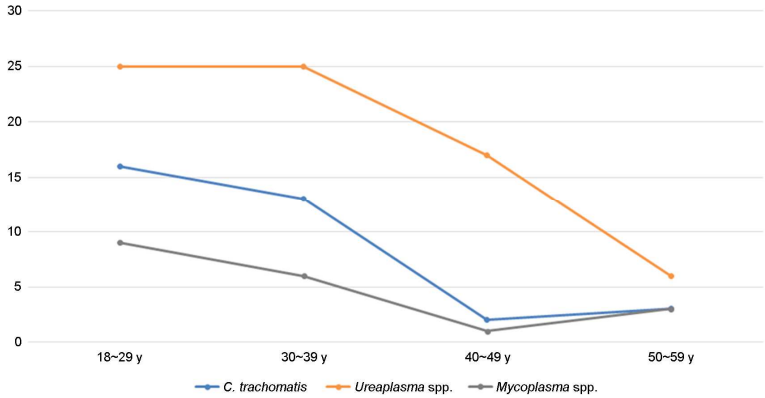

Fig. 2. Distribution of HR-HPV and *Ureaplasma* spp., *C. trachomatis* and *Mycoplasma* spp. Co-infection by age group; HR-HPV and STP co-infection rate was the highest at women aged 18 to 29. HR-HPV and *Ureaplasma* species showed the highest coinfection rates at all ages, followed by *C. trachomatis* and *Mycoplasma* species.

mal cells, leading to cervical cancer (Scheffner et al., 1990; Werness et al., 1990).

Cervical carcinogenesis is not facilitated by HPV infection alone: It is also associated with environmental factors, such as, long-term use of oral contraceptives (Moreno et al., 2002), smoking (Plummer et al., 2003), human immunodeficiency virus (HIV) infection (Ahdieh et al., 2001), and sexually trans mitted pathogens (STPs) other than HPV and HIV (Schmauz et al., 1989). STPs are a cause of serious diseases such as chronic PID, infertility and ectopic pregnancy, and has also been reported as a factor involved in the development of cervical cancer (Ljubin-Sternak and Mestrovic, 2014). STP infection may function as an entryway, allowing the access of HPV to the basal epithelium layer (Samoff et al., 2005; Paba et al., 2008; Paavonen, 2012). STP can induce chronic inflammation, cervical hypertrophy (Markowska et al., 1999; Markowska et al., 2002) and squamous metaplasia, as metaplastic cells are a potential target for the HPV pathogen (Paavonen et al., 2012). Continued infection with HR-HPV by STP infection, especially *Mycoplasma* spp., *C. trachomatis*, and *U. urealyticum* increases the risk of cervical cell degeneration (Silins et al., 2005; Samoff et al., 2005).

Other studies have shown an increased incidence of *Mycoplasma* species, *C. trachomatis*, and *U. urealyticum* infection during HPV infection (Van Der Pol, 2014). In addition, it has been reported the STP infection rate is high in HR-HPV infection. In this study, the positive rate of STP was 52.7% and the negative rate was 47.3% when HPV positive. HPV and STP coinfections were higher in the HR-HPV group (155/187, 82.9%) than in the LR-HPV group (32/187, 17.1%). In HR-HPV infection, *Ureaplasma* spp. was the most common pathogen (73/155, 47.1%), followed by *C. trachomatis* (34/155, 21.9%) and *Mycoplasma* species (19/155, 12.3%). Kim et al. (2016) reported that the incidence of HR-HPV was 1.47 times higher when positive for STP infection than negative. In a large study of 1,218 married women in China, *U. urealyticum* was the most frequently identified pathogen, present in 35.5% of the women examined (Zhang et al., 2017). In Mexico, the HPV and *Ureaplasma* species coinfection rate was 57.7% higher than other STPs (Magana-Contreras et al., 2015). Therefore, it is necessary to follow up the cervical epithelial changes due to HPV and STP coinfection including *Ureaplasma* species.

Recently, mortality from cervical cancer has declined significantly, but the rate of HPV infection in young women has increased sharply (Zhang et al., 2017). In this study, comparing coinfection of HPV and STPs according to age, the rate was found to be the highest among those 18 to 29 years of age (65/155, 41.9%), followed by 30 to 39 years (49/155, 31.6%), 40 to 49 years (26/155, 16.8%), 50 to 59 years (15/155, 9.7%). So, coinfection rates of HPV and STP have decreased with age. These results suggest that high HR-HPV and STP coinfection rates in young women may be a risk factor for chronic cervical disease. Ji (2017) reported that HPV and STP coinfection was associated with cervical neoplasia. Ekiel et al. (2009) reported that *U. urealyticum* is more common in women with HR-HPV infection and occurred more frequently in women with squamous intraepithelial lesions. In the future, it is necessary to observe continuously whether STP infection causes HR-HPV per-

sistent infection and causes cervical lesions.

In conclusion, HR-HPV and STP coinfection was higher in young women aged 18 to 39 years. In particular, continuous monitoring is necessary to prevent the incidence of cervical cancer in patients with coinfection of HR-HPV and *Ureaplasma* spp., *C. trachomatis*, *Mycoplasma* species. Future studies with more specimens will be needed to find the exact association regarding HR-HPV and STP coinfection. In addition, an experiment to analyze the effect of cervical cancer on the development of cervical tumors should be added through a study that contrasts histologic results. Finally, reducing women's HPV and STP infection rates is a shortcut to reduce the incidence of cervical neoplasia.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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