Coinfection of *Ureaplasma urealyticum/Mycoplasma hominis* in HPV Positive Women: Frequency, Risk Factors and Multidrug Resistance

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ABSTRACT Objective: In the development of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN), the most significant cause is high-risk human papillomavirus (HPV) persistence. There are studies reporting high rates of co-prevalent *Ureaplasma urealyticum* in those who have an HPV infection. In this study, *U. urealyticum* positivity and antibiotic resistance rates were investigated in HPV positive women who were asymptomatic in terms of sexually transmitted disease. **Material and Methods:** In this retrospective cohort study, demographic data of the patients with HPV whose cervical swab were sent to the microbiology laboratory for *Mycoplasma* culture were obtained from hospital data management system. *Mycoplasma* culture is done by using a commercial kit (Mycoplasma IES (AutoBio Diagnostics, China) detecting *Mycoplasma hominis* and *U. urealyticum* and antibiotic susceptibility, simultaneously. The demographic data of the cases, HPV test, cervical smear, colposcopy findings and cervical biopsy results were compared according to the *Mycoplasma/Ureaplasma* culture and antibiogram results. Patients with multidrug-resistant *U. urealyticum* were evaluated according to risk factors. **Results:** HPV and *U. urealyticum*, HPV and *M. hominis* coinsidence were found as 43.1% and 1.5%, respectively. No significant difference was found in terms of demographic data. HPV type, cervical smear, colposcopy and cervical biopsy findings were also not correlated with culture positivity. The multidrug-resistant (MDR) *U. urealyticum* ratio was 35.7%. The most resistant and susceptible antibiotics are ciprofloxacin (96.4%) and minocyclin (100%), respectively. In patients with high-risk HPV positive, MDR positivity was significantly higher. **Conclusion:** In this study, it could not find any correlation of HPV type of cases, cervical smear results, colposcopy findings, cervical biopsy results with *U. urealyticum* culture results. Multi-drug resistant *U. urealyticum* (MDR-UU) positivity rates were detected statistically higher in the patients with high-risk-HPV. When HPV positivity is detected in reproductive women, existence of MDR-UU positivity should be considered.

Keywords: HPV, human papilloma virus; MDR; *Ureaplasma urealyticum*; sexually transmitted disease

Cervical cancer has a significant place worldwide in terms of cancer-related deaths in women. In the development of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN), the most important reason is high-risk human papillomavirus (HR-HPV) persistence.[1] Factors such as smoking, high-parity, long-term use of oral contraceptives, other sexually transmitted infectious agents and co-infestation are thought to affect the progression to cervical cancer in HPV infected women.[2,3] The genital mycoplasmas are a class of pathogenic, the smallest free living bacteria in the ciliated epithelial cells of the urinary and genital tract of humans.[4] The genital mycoplasmas colonized in the genital system consist of six types, including *Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, Mycoplasma genitalium, Mycoplasma primatum* and *Mycoplasma spermatophilum*.[5] Some studies have shown that the rate of infection of *U. urealyticum* is high in HPV positive women.[6] Similarly, there are

also different studies reporting co-prevalent *M. hominis* and *U. urealyticum* infection in those with HPV infection. In addition to HPV infection, the rate of *U. urealyticum,* co-infection was reported to be 19.5% in asymptomatic sexually active women.[7]

Although *U. urealyticum* co-infection with HPV is not uncommon, the biological role of *U. urealyticum* in HPV infection is not clearly understood. *U. urealyticum* is thought to be a cofactor in the development of HPV-mediated cervical dysplasia.[8] *U. urealyticum* may play a role in the onset of viral persistence and cellular anomalies.[9,10] There are studies showing that Mycoplasma infection causes in vitro chromosomal changes and cell transformation, chromosomal loss, translocation.[11] Similarly, in the presence of *Mycoplasma* infection, Robertsonian described chromosomal translocations.[12] In this study, *U. urealyticum* positivity, antibiotic resistance rates and related risk factors were investigated in HPV positive women who are asymptomatic in terms of sexually transmitted disease.

█ MATERIAL AND METHODS

This retrospective cohort study was conducted between January 2020 and April 2020 at Kütahya Health Sciences University Evliya Celebi Training and Research Hospital after ethics approval of the study was obtained from the Non-interventional Research Ethics Committee of Kütahya University of Health Sciences (2020/06-10).

The patients between 25-62 years of age were sexually active and had no symptoms regarding sexually transmitted disease. Pregnant women and the women who had a hysterectomy, the ones receiving vaginal treatment within 3 days of cervical sampling, the ones who have been treated for cervical disease (such as LEEP) for the past 6 months, and those with vaginal or urethral discharge, itching in the external genital organs, dyspareunia, dysuria, vaginal bleeding in the form of spotting, haematuria and antibiotic users within fifteen days were not included in the study

The demographic data including age, body mass index (BMI), age of the first delivery, education level, marital status and laboratory data of the women 25-

62 years of age who were detected positivity therefore referred from Cancer Early Diagnosis Screening and Training Centre (CEDSTC) to Gynaecological Oncology Outpatient Clinic were analysed. The women applied to Gynaecological Oncology Outpatient Clinic with their HPV and Papanicolaou (Pap) smear test reports were taken cervical swab sample for *Mycoplasma* culture. Demographic data, HPV test, cervical smear, colposcopy findings and cervical biopsy results of the cases were compared according to *U. urealyticum* growth.

Pap smear results were classified according to the Bethesda system as "negative in terms of malignancy and intraepithelial lesion", "atypical squamous cells of undetermined significance (ASC-US)", "low-grade squamous intraepithelial lesion (LSIL)" and "high grade squamous intraepithelial lesion (HSIL)".[13] The colposcopic examination results were grouped as "no lesion", "acetowhite epitel", "punctuation", "mosaism". In the cervical biopsy, intraepithelial lesions were classified as CIN I, II, III according to the degree of dysplasia.[14]

The colposcopy indications of our clinic were performed according to The American Society for Colposcopy and Cervical Pathology Colposcopy Standarts: abnormal or inconclusive Pap smear test, abnormality found during pelvic examination, abnormal genital tract bleeding, or unexplained cervicovaginal discharge and past cytologic and/or pathologic anogenital tract abnormalities.[15]

HUMAN PAPILLOMAVIRUS SCREENING

The patients applied to the institution with HPV screening. In (CEDSTC) HPV sampling of the patients was done with the Digene HPV HC2 DNA test kit (Qiagen, Hilden, Germany) on the DML 3000 luminometer device. It was learned that HPV typing of positive cases was determined by applying PCR using EZ1 virus mini kit (Qiagen, Hilden, Germany). 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 83 were accepted as HR-HPV types. 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81 were accepted as low-risk-HPV (LR-HPV) types.

MYCOPLASMA HOMINIS AND *UREAPLASMA UREALYTICUM* SCREENING

Detection of *M. hominis* and *U. urealyticum* in the genitourinary system samples, identification and antibiotic susceptibility tests were performed using the Mycoplasma IES (AutoBio Diagnostics, China) kit in the microbiology laboratory. Based on the bacterial production and biochemical reactions, the blend medium of the kit was prepared in accordance with the package insert, by mixing frozen-dry powder and diluent.Thanks to the enzymes that break down urea and *M. hominis* arginine of *U. urealyticum*, the result was evaluated on the basis of increasing the pH in the liquid medium of NH3 and the colour change of the indicator. Also, the sensitivity of Clinical & Laboratory Standards Institute (CLSI) to 11 antibiotics from three groups recommended for antibiogram was tested. Since it was naturally resistant to *U. urealyticum* clindamycin, it was not evaluated in statistical analysis. In the data evaluated retrospectively, the susceptibility levels were analysed by accepting low susceptible strains as resistant.

STATISTICAL ANALYSIS

SPSS® software (SPSS 15.0, SPSS, Chicago, IL, USA) was used for statistical analysis.The suitability of the data for normal distribution was determined by the Shapiro-Wilk test. Variables were expressed as mean±standard deviation or median (Q25-Q75). Continuous variables were compared with Student t-test or Mann-Whitney U test. Categorical variables were compared with chi-square test or Fisher's exact test. In the comparison of ordered categorical variables, Mantel-Haenszel chi-square test was used. $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the cases was calculated as 43.8±8.7 years. When the demographic data of the cases were compared according to the *U. urealyticum* culture result, no significant difference was found in terms of age, height, weight, first coitus age, total number of partners, age of first birth, education level, marital status, use of contraception method, vaginal douche, infertility, chronic disease, operation, medication use (e.g antihypertensive), smoking, menopause history

$(p>0.05)$. Demographic data are given in Table 1. In this study, in HPV positive women who are asymptomatic in terms of sexually transmitted diseases, *U. urealyticum* positivity rate was found to be 43.1%. In addition to *U. urealyticum* in 1 (1.5%) case, *M. hominis* was also found positive.

When the HPV type of the cases, cervical smear result, colposcopy findings and cervical biopsy results were compared according to the *U. urealyticum* culture result, no significant difference was found $(p>0.05)$. HPV type, cervical smear result, colposcopy findings and cervical biopsy results are given in Table 2.

In 28 (43.1%) of the cervical swab samples taken from the patients, $\geq10^4$ CFU/mL *U. urealyticum* reproduced. When antibiotic susceptibility test results are evaluated, the most sensitive antibiotics were minocycline (100%), erythromycin and josamycin (82.1%), levofloxacin (78.6%) and roxithromycin (71.4%), respectively. The antibiotics that this bacterium is most resistant to was determined as ciprofloxacin (96.4%) and ofloxacin (53.6%) (Table 3). The multidrug-resistant (MDR) UU ratio of at least one antibiotic-resistant from each of the tested tetracycline, macrolide and quinolone group antibiotics was 35.7% (n=10).

No statistical difference was found between MDR-UU positivity and demographic and other features $(p>0.05)$. MDR-UU positivity rates were to be higher in the patients with high risk-HPV (p=0.049) (Table 4)

DISCUSSION

In this study, *U. urealyticum* positivity rate was found to be 43.1% in HPV positive women who were asymptomatic in terms of sexually transmitted disease. When the HPV type, cervical smear result, colposcopy findings and cervical biopsy results were compared in terms of the *U. urealyticum* culture result, no significant difference was found.

The most important reason for the development of cervical cancer and its precursor, CIN, is a HR-HPV persistence.[1] The causality relationship between cervical cancer and HPV is clear. However, it is thought that facilitating factors are needed for HPV

TABLE 1: Comparison of the demographic data of the cases according to the *Ureaplasma urealyticum* culture result.

		U. urealyticum				
		Negative		Positive		
		Mean	Standard deviation	Mean	Standard deviation	p
Age (year)		45.3	9.9	41.8	6.3	0.086[a]
Height (cm)		158.2	5.3	158.1	5.8	0.968[a]
Weight (kilogram)		67.5	12.6	69.3	16.9	0.947[b]
Age at first coitus (year)		19.1	3.1	19.4	3.7	0.584[b]
Total number of partners		1.2	0.6	1.7	1.6	0.111[b]
Age at first delivery (year)		21.4	4.0	22.2	4.5	0.446[b]
		n	%	n	%	
Education level	Illiterate	4	10.8	1	3.6	0.854[c]
	Primary school	19	51.4	17	60.7	
	Middle school	4	10.8	3	10.7	
	High school	8	21.6	5	17.9	
	Two-years degree	1	2.7	0	0.0	
	Bachelor' degree	1	2.7	2	7.1	
Marital status	Married	32	86.5	21	75.0	0.338[c]
	Single	0	0.0	1	3.6	
	Divided	5	13.5	6	21.4	
Using contraception method	No	20	54.1	13	46.4	0.883[c]
	Condom	7	18.9	7	25.0	
	OKP	2	5.4	2	7.1	
	IUD	3	8.1	4	14.3	
	Coitus interruptus	2	5.4	1	3.6	
	BTL	3	8.1	1	3.6	
Vaginal douche	Yes	29	78.4	20	71.4	0.520[c]
	No	8	21.6	8	28.6	
Infertility	No	33	89.2	24	85.7	0.717[d]
	Yes	4	10.8	4	14.3	
Chronic disease	No	24	64.9	13	46.4	0.137[c]
	Yes	13	35.1	15	53.6	
Operation history	No	16	43.2	16	57.1	0.267[c]
	Yes	21	56.8	12	42.9	
Medication use	No	25	67.6	16	57.1	0.388[c]
	Yes	12	32.4	12	42.9	
Smoking	No	26	70.3	20	71.4	0.919[c]
	Yes	11	29.7	8	28.6	
Menopause status	Premenopause	26	70.3	23	82.1	0.271[c]
	Postmenopause	11	29.7	5	17.9	

OCP: Oral contraceptive pills, IUD: Intrauterine device, BTL: Bilateral tubal ligation.
[a]Student t-test, [b]Mann-Whitney U test, [c]Chi-square test, [d]Fisher's exact test.

infection to cause cervical cancer. These facilitating factors include many sexual partners and environmental factors such as sexually transmitted diseases.[8]

Most studies argue that *Mycoplasma/Ureaplasma* infection positivity increases the likelihood of acquiring HPV infection. *U. urealyticum* and *M. genitalium* are the most common species having coincidence with HPV infection.[7,16,17] In the study conducted by Kim et al., *U. urealyticum* ($>10^4$ CFU/mL), which forms a high-density colony, was associated with HPV infection.[7] Verteramo et al., and Ekiel et al. stated that *U. urealyticum* ($>10^4$ CFU/mL) may be a risk factor for HPV infection in asymptomatic women.[6,7,18] Lukic et al,. reported that the presence of *U. urealyticum* ($>10^4$

TABLE 2: Comparison of cases with HPV type, cervical smear result, colposcopy findings and cervical biopsy results in terms of *Ureaplasma urealyticum* culture result.

		U. urealyticum				
		Negative		**Positive**		
		n	%	n	%	p
HPV type						
	High-risk	32	88.9	22	78.6	0.259[a]
	Low-risk	4	11.1	6	21.4	
Cervical smear result						
	Intraepithelial lesion negative	23	63.9	15	53.6	0.544[b]
	ASCUS*	7	19.4	9	32.1	
	LSIL**	6	16.7	4	14.3	
	HSIL***	0	0.0	0	0.0	
Colposcopy findings	No lesion	11	29.7	4	14.3	0.343[a]
	Acetowhite epithelium	13	35.1	12	42.9	
	Punctuation	13	35.1	12	42.9	
	Mosaicism	0	0.0	0	0.0	
Cervical biopsy result	Chronic cervicitus	25	67.6	15	53.6	0.323[b]
	CIN****	7	18.9	9	32.1	
	CIN II-III	5	13.5	4	14.3	

HPV: Human papilloma virus, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia.
[a]Chi-square test, [b]Mantel-Haenszel chi-square test.

CFU/mL) in women might be a cofactor for HPV and adversely affect the results of cervical cytology.[9] In the study of Biernat-Sudolska et al., they showed that the rate of detection of *U. urealyticum* in cases with cervical cancer is higher than women with normal cytology.[19] Pisani et al., found a positive relationship between *U. urealyticum* and HPV infection and claimed that *Ureaplasma urealyticum* and HPV might have a synergistic effect in the formation of CIN and cervical cancer.[20] However, in this study, *U. urealyticum* did not affect cervical cytology results.

Lopez-Arias et al., found a correlation between *M. hominis*/*U. urealyticum* and high risk-HPV infection, but could not find a relationship between the severity of *U. urealyticum* coinfection and cervical lesions.[21] On the contrary, in the cervical microbial environment study investigating the factors affecting HPV clearance rates, the presence of *U. urealyticum* was shown to increase HPV clearance.[22] In this study, no relation was found between *U. urealyticum* and high risk-HPV coinfection and severity of cervical lesions.

In the literature, *U. urealyticum* rates differ in HPV positive women. In the study of Kim et al., they reported the prevalence of *U. urealyticum* as 36%,

TABLE 3: *Ureaplasma urealyticum* antibiotic susceptibility rates.

	Susceptible		**Resistant**	
	n	%	n	%
Minocycline	28	100		
Tetracycline	15	53.6	13	46.4
Erythromycin	23	82.1	5	17.9
Clarithromycin	17	60.7	11	39.3
Roxithromycin	20	71.4	8	28.6
Josamycin	23	82.1	5	17.9
Ofloxacin	13	46.4	15	53.6
Ciprofloxacin	1	3.6	27	96.4
Levofloxacin	22	78.6	6	21.4

and the coincidence of *U. urealyticum* with HPV as 19.5%.[7] Zhang et al. reported the prevalence of *Ureaplasma urealyticum* as 35.5%, and HPV and *Ureaplasma urealyticum* coincidence as 8.6% in symptomatic women.[10] Lv et al. found the prevalence of *U. urealyticum* as 15.4% in women with HR-HPV positive, and 8.6% in *U. urealyticum* in women with HR-HPV negative.[23] Parthenis et al.also found that the rate of positive HR-HPV types was 25.4% and the positive rate of LR-HPV types was 7.9% in women who had positive *Ureaplasma* test.[17] Lopez-Arias et al., reported *U. urealyticum* coincidence with HPV as

TABLE 4: Evaluation of risk factors for multidrug-resistant *Ureaplasma urealyticum.*					
		No multidrug-resistant UU (n=18)		Multidrug-resistant UU (n=10)		
		Mean	Standard deviation	Mean	Standard deviation	p
Age (year)		42.5	5.72	40.4	7.41	0.449[a]
BMI (kg/m²)		26.54	3.98	29.57	8.6	0.318[a]
		n	%	n	%	
Education level	Middle School or below	14	66.7%	7	33.3%	0.674[b]
	High School and above	4	57.1%	3	42.9%	
Marital status	Married	14	66.7%	7	33.3%	0.674[b]
	Single	4	57.1%	3	42.9%	
Vaginal douche	Yes	13	65%	7	35%	1.000[b]
	No	5	62.5%	3	37.5%	
Infertility history	No	15	62.5%	9	37.5%	1.000[b]
	Yes	3	75%	1	25%	
Operation history	No	11	58.3%	5	31.3%	0.698[b]
	Yes	7	56.8%	5	41.7%	
Medicine use	No	11	68.8%	5	31.3%	0.698[b]
	Yes	7	58.3%	5	41.7%	
Smoking	No	14	60.9%	9	39.1%	0.400[b]
	Yes	4	80%	1	20.0%	
Menopausal status	Premenopausal	14	60.9%	9	39.1%	0.271[b]
	Postmenopausal	4	80%	1	20%	
HPV	High-risk	12	54.5%	10	45.5%	0.049[b]
	Low-risk	6	100%	0	0%	

BMI: Body mass index, HPV: Human papillomavirus.
[a]Mann-Whitney U test, [b]Chi-square test.

16.7%.[21] In the study of Biernat-Sudolska et al., *Ureaplasma* and/or *Mycoplasma* coinfection rate with HPV was reported as 24%.[19] In the same study, they reported the *M. hominis* prevalence as 1%. In this study, in HPV positive women, *U. urealyticum* positivity rate was found to be 43.1%, *M. hominis* prevalence was 1.5% in line with the literature.

Since *Mycoplasmas'* do not have a rigid cell wall, they are naturally resistant to beta-lactam antibiotics and vancomycin. *U. urealyticum* is also naturally resistant to lincosamides, thereby macrolides, quinolones and tetracyclines, which are protein synthesis inhibitors, are often used in treatment. Also, it showed resistance to these drugs at various rates. Besli et al., reported that antibiotics with the highest susceptibility rates for *U. urealyticum* detected in the samples of the genitourinary system were minocycline (98.5%), doxycycline (98.1%) and josamycin (98.1%).[24] Bayraktar et al., found 100% sensitivity to doxycycline, tetracycline and pristinamine, 92.6% to josamine and 88.9% to clarithromycin, and found the

highest resistance against ciprofloxacin (92.6%) and ofloxacin (85.2%).[25] Khan et al., found minocycline and doxycycline as the most effective antibiotics, and the activity of erythromycin to be quite high, and the highest resistance against tetracycline.[26] Michael et al., found that levofloxacin and moxifloxacin were more effective than ciprofloxacin, and all strains were susceptible to macrolides (erythromycin and azithromycin).[27] In line with the literature, in this study, it was found that minocycline had a significantly higher susceptibility compared to tetracycline, and levofloxacin was significantly more susceptible than other quinolones (ofloxacin and ciprofloxacin) (78.6% vs. 46% and 3.6%), and except for clarithromycin, which is one of the macrolides, was similarly susceptible (78.6% vs. 82.1%). In this study, due to the lack of HPV negative control group, it was not found whether *U. urealyticum* coinfection increased the risk of developing a HPV infection. Also, the case number in this study was relatively low. These factors can be considered as limitations of the study.

CONCLUSION

In this study, no correlation of HPV type of cases, cervical smear results, colposcopy findings, cervical biopsy results with *U. urealyticum* culture results. MDR-UU positivity rates were detected statistically were found higher in the patients with HR-HPV. When HPV positivity is detected in reproductive women, existence of MDR-UU positivity should be considered.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: İsmail Bıyık, Nadi Keskin, Özlem Erten; Design: İsmail Bıyık, Aynur Gülcan, Nadi Keskin, Halil İbrahim Şişman; Control/Supervision: İsmail Bıyık, Onur İnce, Aynur Gülcan; Data Collection and/or Processing: İsmail Bıyık, Nadi Keskin, Halil İbrahim Şişman; Analysis and/or Interpretation: İsmail Bıyık, Onur İnce, Aynur Gülcan; Literature Review: İsmail Bıyık, Özlem Erten, Aynur Gülcan; Writing the Article: İsmail Bıyık, Aynur Gülcan; Critical Review: Nadi Keskin, Özlem Erten; References and Fundings: Halil İbrahim Şişman.

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