Research Paper

Co-infection Of Ureaplasma urealyticum And Human Papilloma Virus In Asymptomatic Sexually Active Individuals

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Abstract

This study aimed to determine the role of asymptomatic bacterial sexually transmitted infections (STIs), such as Chlamydia trachomatis (Ct), Mycoplasma genitalium (Mg), Mycoplasma hominis (Mh), and Ureaplasma urealyticum (Uu) in human papillomavirus (HPV) infection.

In total, 264 asymptomatic outpatients aged between 21 and 80 years were prospectively enrolled in this study during routine gynecological screening tests. Specimens collected with a Cervex Brush were routinely analyzed with the Hybrid Capture 2 assay for HPV. Simultaneously, a specimen obtained with an endocervical swab was used to detect Ct and Mg with a monoplex real-time polymerase chain reaction (PCR) and to confirm Mh and Uu with a Mycoplasma IST 2 kit.

The detection rates (%) of HPV, Ct, Mg, Mh, and Uu were 82/264 (31.1), 6/264 (2.3), 5/264 (1.9), 16/264 (6.1), and 95/264 (36.0), respectively. Of 95 Uu, 32 (33.7%) showed high density colonization (HDC, ≥10⁴ color-changing units/mL). HDC-Uu was significantly associated with HPV infection (p=0.014, chi-square test). Mg infection and Mh infection were not associated with HPV infection (p=0.981 and p=0.931, chi-square test). Age was not associated with HPV infection or bacterial infection.

Our data suggested that asymptomatic HDC-Uu was closely associated with HPV infection. Therefore, simultaneous evaluation for Uu and HPV should be performed during gynecological screening, even in asymptomatic individuals.

Key words: Mycoplasma; Ureaplasma urealyticum; human papillomavirus

Introduction

Human papillomavirus (HPV) has been identified the etiologic agent of warts, cervical intraepithelial neoplasia (CIN), and cervical cancer. Among sexually transmitted infections (STIs), only HPV infection is known to be a major cause of cervical cancer.1 However, cervical carcinogenesis is not facilitated by HPV infection alone, but it also associated with environmental factors, such as multiple sex partners and sexually transmitted diseases.2

A Recent study investigated the relationships between HPV and vaginal bacteria, including Mycoplasma spp. and Chlamydia trachomatis (Ct), and found that HPV was associated with Ct and Ureaplasma urealyticum (Uu).3 Therefore, detection of Mycoplasma or Chlamydia infection may play a role in decreasing the prevalence of cervical cancer. Although, the majority of individuals infected with Chlamydia and Mycoplasma were asymptomatic,4,5 they could be carriers of Chlamydia and Mycoplasma infections in the community. A recent study
conducted in Korea showed an incidence (%) of 5.6, 0.3, 22.1 and 11.6, respectively, for Ct, M. genitalium (Mg), Uu, and M. hominis (Mh) in asymptomatic individuals. However, to our knowledge, no epidemiologic study has evaluated the association between asymptomatic bacterial STIs and HPV infection in sexually active individuals.

The aim of this study was to evaluate the relationship between bacterial STI and HPV infection among asymptomatic sexually active women.

Materials and methods

Study population

From a group of asymptomatic women who visited a gynecological outpatient clinic for routine screening between January 2012 and August 2017, 264 volunteers were enrolled in this study. Informed consent was obtained from all women participating in the study. The institutional review board of The Catholic University of Korea approved this study (No. VC15RISI0094). Cervical specimens for high-risk HPV detection and identification of other microorganisms were taken from the asymptomatic volunteers during a routine pelvic examination. Cytology was graded according to the Bethesda system, using standard forms, and was classified as negative, low-grade (atypical squamous cells of undetermined significance, atypical glandular cells of undetermined significance, low-grade squamous intraepithelial lesion), or high-grade (atypical squamous cells - cannot exclude high-grade squamous intraepithelial lesion).

All women aged between 21 and 80 years who engaged in sexual activity at least once a month were eligible. Exclusion criteria were: 1) any urogenital symptoms, such as vaginal and/or urethral discharge, itching at the external genitalia, dyspareunia, dysuria, vaginal spotting, or hematuria; 2) antimicrobial treatment within 1 month prior to the present study; 3) recently diagnosed cervical disease within 6 months prior to the present study; 4) current pregnancy.

All participants were interviewed regarding obstetric history and the number of sexual partners in the prior 2 years.

HPV detection

Specimens were collected with a Cervex Brush (Rovers Medical Devices B.V., The Netherlands) and rinsed with PreservCyt fixative solution (Cytocorp., Roxborough, MA, USA). Specimens were placed in denatured alcohol at 65 ± 2°C for 45 min, and mixed with a 1:25 diluted HPV probe (for high-oncogenic risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) in a 96-well plate with the help of a rotary shaker at 1,100 rpm. The mixture was incubated at 65 ± 2°C for 60 min. The hybridized mixture was moved a Capture micro-plate (Digene Corp., Gaithersburg, MD, USA), with shaking at 1,100 rpm at 20-25°C for 60 min. Finally, the conjugation process was performed by adding the detection reagent (CDP-Star®, Tropix, Inc., MA, USA) to the Capture micro-plate. After the washing process, the test result was reported in relative light units using a DML 2000 Luminometer (Qiagen, Crawley, UK).

Detection of other microorganisms

The swab specimen in the collection tube was equilibrated to room temperature and mixed by vortexing. After centrifugation at 13,000 rpm for 10 min, the supernatant was discarded and the pellet was re-suspended in 1 ml of 1× phosphate-buffered saline by vortexing thoroughly to re-dissolve and disperse the sample. The mixed specimen was transferred to 1.5 ml Eppendorf tubes. DNA was then extracted from the pretreated specimens using the QIAamp® DNA Mini Kit (QIAGEN, Hilden, Germany), according to the manufacturer's instructions. Ct and Mg were detected with a monoplex polymerase chain reaction (PCR) using Seegene DPO™ technology. PCR amplification was performed with the Seeplex® C. trachomatis Detection kit and Seeplex® M. genitalium Detection kit (Seegene, Seoul, Korea) according to the manufacturer’s instructions.

Both Mh and Uu were detected using the commercially available Mycoplasma IST 2 kit (bioMérieux, Marcy-l’Étoile, France). Using this kit, we detected Mh and/or Uu at a cut-off value of 10⁴ color-changing units (CCU)/mL. A positive test was indicated by a change in broth color from yellow to red (urea for Uu and arginine for Mh). An endocervical swab specimen was inoculated into the R1 solution (transport medium) according to the manufacturer’s instructions, then combined with a vial of R2 (lyophilized growth medium) and vortexed. A 55-µL aliquot of the solution was dispensed into each of 22 test wells on the strip. Two drops of mineral oil were added to each well. The strips were incubated at 37.8°C for 24-48 h. Antimicrobial susceptibility against doxycycline, josamycin, ofloxacin, erythromycin, tetracycline, ciprofloxacin, azithromycin, clarithromycin and pristinamycin was also tested using this commercial kit.

However, U. parvum (biovar 1) and Uu (biovar 2) could not be discriminated with this kit. Therefore, we used Uu for both biovars as in previous research.

Statistical analysis

SPSS® software (SPSS 15.0, SPSS, Chicago, IL, USA) was used for the statistical analysis. Student’s
t-test, the chi-squared test, and Fisher’s exact test, were used for statistical evaluations of the associations between groups using nominal data. Logistic regression was used for multivariate analysis and \( p < 0.05 \) was considered statistically significant.

**Results**

The mean age of participants was 50.76 ± 11.04 years and the mean body mass index (kg/m²) was 23.04 ± 4.19. Baseline participant characteristics are presented in Table 1. Among epidemiologic factors, 2 or more sexual partners in the prior 2 years showed a greater association with current HPV infection than 1 partner \( (p=0.001, \text{chi-square test}) \). Obstetric history was not significantly associated with current HPV infection.

The incidences (%) of HPV, Ct, Mg, Uu \(<10^4\) CCU/mL, high-density colonization (HDC)-Uu \(<10^4\) CCU/mL), Mh \(<10^4\) CCU/mL, and HDC-Mh \(<10^4\) CCU/mL in the present study was 31.1, 2.3, 1.9, 23.9, 12.1, 4.9, and 1.1, respectively. Among the 264 asymptomatic volunteers, HPV tested positive in 82 (31.1%) and 69 (26.1%) had abnormal cytology. HPV infection and both low- and high-grade cytologic abnormalities, were not associated with patient age. Bacterial infections were also not related to patient age. The distribution of HPV infection, cytologic abnormalities, and bacterial infections according to age is shown in Table 2.

Two Ct infections \( (2/6) \) were found in the HPV-infected group \( (p=0.903, \text{chi-square test}) \). HDC-Uu \((>10^4\) CCU/mL) was significantly associated with HPV infection \( (p=0.014, \text{chi-square test}) \). Even after adjusting for confounding epidemiologic factors, such as multiple sexual partners \( (\geq 3) \), HDC-Uu was still significantly associated with HPV infection \( (p=0.045, \text{logistic regression analysis}) \). Uu \((<10^4\) CCU/mL) was not associated with HPV infection \( (p=0.284, \text{chi-square test}) \). Mg and Mh (both \(<10^4\) CCU/mL) were also not associated with HPV infection \( (p=0.158 \text{ and } p=0.981, \text{respectively, chi-square test}) \). The distribution of each microorganism is shown according to the presence of HPV infection in Table 3.

Antimicrobial susceptibility testing of Uu showed that the microorganisms were resistant to fluoroquinolones, such as ofloxacin and ciprofloxacin. Meanwhile, Mh tended to be resistant to macrolides such as erythromycin, azithromycin and clarithromycin (Table 4).

### Table 1. Baseline characteristics of study population \((N=264)\)

| Characteristic                        | HPV negative \((n=182)\) | HPV positive \((n=82)\) | Total \((n=264)\) | OR \(\text{OR}^*\) | \(p\)-value, 95% CI |
|---------------------------------------|--------------------------|-------------------------|-------------------|------------------|-------------------|
| Age (mean)                            | 51.5±8.06                | 49.1±12.55              | 50.7±11.04        | 0.376            | 0.223 ~ 0.586     |
| Number of partners                    |                          |                         |                   |                  |                   |
| 1 partner                             | 155 (85.2%)              | 39 (47.6%)              | 194 (75.5%)       | 1.00             |                   |
| 2 partners                            | 14 (7.7%)                | 20 (24.4%)              | 34 (12.9%)        | 5.678            | 0.001, 2.634 ~ 12.24 |
| 3 or more partners                    | 13 (7.1%)                | 23 (28.0%)              | 36 (13.6%)        | 7.032            | 0.001, 3.270 ~ 15.12 |
| Parity                                |                          |                         |                   |                  |                   |
| Nulliparous                           | 43 (23.6%)               | 22 (26.8%)              | 65 (24.8%)        | 1.00             |                   |
| Multiparous                           | 139 (76.4%)              | 60 (73.2%)              | 199 (75.4%)       | 1.54             | 0.330, 0.641 ~ 3.715 |
| Abortion                              | 25 (13.7%)               | 23 (28.0%)              | 48 (18.2%)        | 2.29             | 0.198, 0.752 ~ 6.948  |

Each mean data was presented with standard deviation

\(\text{OR}^*\) is the odds ratio compared with the first category, and \(\text{OR}^\dagger\) is the odds ratio between HPV negative and positive group.

\(p\)-value\(^*\) and \(p\)-value\(^\dagger\) were measured by \(t\)-student test and Chi-square test, respectively.

### Table 2. Characteristics of human papillomavirus infection, cervical cytology and sexually transmitted bacterial infection by age \((N=264)\)

| Age distribution | 21–50 \((n=139)\) | 51–80 \((n=125)\) | OR | \(p\)-value | 95% CI |
|------------------|-------------------|-------------------|----|-------------|-------|
| HPV              |                   |                   |    |             |       |
| HPV negative \((n=182)\) | 93/139 (66.9%) | 89/125 (71.2%) | 1.00 |             |       |
| HPV positive \((n=82)\)    | 46/139 (33.1%) | 36/125 (28.8%) | 1.223 | 0.4516 | 0.724 ~ 1.652 |
| Cytology          |                   |                   |    |             |       |
| Negative cytology \((n=195)\) | 101/139 (72.6%) | 94/125 (75.2%) | 1.00 |             |       |
| Low grade abnormality\(^t\) \((n=28)\) | 14/139 (10.1%) | 14/125 (11.2%) | 0.888 | 0.766 | 0.406 ~ 1.945 |
| High grade abnormality\(^t\) \((n=41)\) | 24/139 (17.3%) | 17/125 (13.6%) | 1.326 | 0.412 | 0.675 ~ 2.603 |
| Bacterial infection |                   |                   |    |             |       |
| *Chlamydia trachomatis* \((n=6)\) | 4/139 (2.9%) | 2/125 (1.6%) | 1.822 | 0.487 | 0.328 ~ 10.13 |
| *Mycoplasma genitalium* \((n=5)\) | 4/139 (2.9%) | 1/125 (0.8%) | 3.674 | 0.216 | 0.405 ~ 33.34 |
| *Ureaplasma urealyticum* \((n=95)\) | <10CCU/mL \((n=63)\) | 32/139 (23.0%) | 31/125 (24.8%) | 0.907 | 0.759 | 0.515 ~ 1.598 |
| *Mycoplasma hominis* \((n=16)\) | >10CCU/mL \((n=52)\) | 18/139 (12.9%) | 14/125 (11.2%) | 1.179 | 0.664 | 0.560 ~ 2.483 |
| *Mycoplasma hominis* \((n=16)\) | =10CCU/mL \((n=13)\) | 4/139 (2.9%) | 9/125 (7.2%) | 0.382 | 0.105 | 0.115 ~ 1.273 |
| *Mycoplasma hominis* \((n=5)\) | >10CCU/mL \((n=5)\) | 1/139 (0.7%) | 2/125 (1.6%) | 0.446 | 0.500 | 0.040 ~ 4.978 |

Data in bracket was presented as positive cases/all cases, percentage

\(^t\) Chi-squared test; \(^t\) Low grade: ASCUS, AGUS, LSIL; \(^t\) High grade: ASC-H, HSIL
asymptomatic patients. Lukic et al. emphasized that HDC-association between delayed in a symptomatic women, but not in Coinfection of \textit{Uu} with HPV contributes to development of CIN. Diagnosis and treatment can be \textit{Uu} in asymptomatic, sexually active woman at all age.

Verteramo et al. suggested that \textit{U. urealyticum} and \textit{C. trachomatis} influence on cervical cytology.

The number of sexual partners is a known risk factor for HPV infection, Kataja et al. reported that the number of sexual partners during prior 2 years is the strongest independent risk factor for HPV infections. In our cohort, we tried to classify participants according to the number of sexual partners in the present study.

Zhang et al. found that \textit{Uu} was the most common infection among patients with HPV, which supports our result. However, in contrast to our results, there was no significant association between \textit{Uu} and HPV infection.

Other studies suggesting a relationship between HPV infection and \textit{Uu} infection are described in table 5,3,10,12-20 These studies strongly support an association between \textit{Uu} and HPV infection. Coinfection of \textit{Uu} with HPV contributes to development of CIN. Diagnosis and treatment can be delayed in asymptomatic women, but not in symptomatic women with \textit{Uu} and HPV coinfection. Therefore, HPV testing is suggested in women with \textit{Uu} infection, regardless of symptom status.

The number of sexual partners is a known risk factor for HPV infection, Kataja et al. reported that the number of sexual partners during prior 2 years is the strongest independent risk factor for HPV infections. In our cohort, we tried to classify participants according to the number of sexual partners in the present study.

Kataja et al. reported that the risk for HPV infection varied with age, being highest in the 20-29 year old group, and thereafter declining in subsequent 10-year age groups.

However, in our cohort, we found no relationship between age and HPV infection. Moreover, age was not associated with abnormal cytology or bacterial infection. Therefore, asymptomatic infection with HDC-\textit{Uu} should be eradicated, regardless of age, for the prevention of HPV infection and subsequent CIN.

### Table 3. Relationship between sexually transmitted bacterial infections and HPV infection (N=264)

| Bacterial infection | HPV negative (n=182) | HPV positive (n=82) | p-value, OR, 95% CI |
|---------------------|----------------------|---------------------|---------------------|
| \textit{C. trachomatis} (n=6) | 4 (2.2%) | 2 (2.4%) | 0.905; 1.113-0.199-6.202 |
| \textit{M. genitalium} (n=5) | 2 (1.1%) | 3 (3.7%) | 0.158; 3.418-0.559-20.86 |
| \textit{U. urealyticum} (n=95) | <10^4 CCU/ml (n=63) | 40 (22.0%) | 23 (28.0%) | 0.284; 1.384-0.762-2.512 |
| | >10^4 CCU/ml (n=32) | 16 (8.8%) | 16 (19.5%) | 0.014; 2.515-1.189-5.322 |
| \textit{M. hominis} (n=16) | <10^4 CCU/ml (n=13) | 9 (4.9%) | 4 (4.9%) | 0.981; 0.985-0.294-3.299 |
| | >10^4 CCU/ml (n=3) | 2 (1.1%) | 1 (1.2%) | 0.931; 1.111-0.099-12.44 |

Each value was presented as negative/positive.

*Chi-squared test
†Chlamydia trachomatis
§Mycoplasma genitalium
∥Ureaplasma urealyticum
‡Mycoplasma hominis

### Table 4. Antimicrobial susceptibility pattern of \textit{Ureaplasma urealyticum} and \textit{Mycoplasma hominis} in asymptomatic sexually active women (N=111*)

| Bacterial infection | Susceptible (n=95) | Intermediate (n=16) | Resistant (n=82) |
|---------------------|--------------------|--------------------|-----------------|
| \textit{Ureaplasma urealyticum} (n=95) | Sr (%) | I (%) | R (%) |
| Doxycycline | 95 (100.0) | 0 (0.0) | 0 (0.0) |
| Josamycin | 95 (100.0) | 0 (0.0) | 0 (0.0) |
| Ofloxacin | 38 (40.0) | 48 (50.5) | 8 (8.4) |
| Erythromycin | 83 (87.4) | 10 (10.5) | 2 (2.1) |
| Tetracycline | 95 (100.0) | 0 (0.0) | 0 (0.0) |
| Ciprofloxacin | 10 (10.5) | 39 (41.1) | 46 (48.4) |
| Azithromycin | 77 (81.0) | 18 (18.9) | 0 (0.0) |
| Clarithromycin | 93 (97.9) | 0 (0.0) | 2 (2.1) |
| Pristinamycin | 95 (100.0) | 0 (0.0) | 0 (0.0) |

| \textit{Mycoplasma hominis} (n=16) | Sr (%) | I (%) | R (%) |
| Doxycycline | 16 (100.0) | 0 (0.0) | 0 (0.0) |
| Josamycin | 16 (100.0) | 0 (0.0) | 0 (0.0) |
| Ofloxacin | 14 (87.5) | 2 (12.5) | 0 (0.0) |
| Erythromycin | 2 (12.5) | 2 (12.5) | 0 (0.0) |
| Tetracycline | 16 (100.0) | 0 (0.0) | 0 (0.0) |
| Ciprofloxacin | 11 (68.8) | 4 (25.0) | 2 (12.5) |
| Azithromycin | 14 (87.5) | 12 (75.0) | 0 (0.0) |
| Clarithromycin | 95 (100.0) | 0 (0.0) | 0 (0.0) |

*Among 264 patients, 95 patients were positive for \textit{Ureaplasma urealyticum} and 16 patients were positive for \textit{Mycoplasma hominis}. Antibiotics susceptibility was tested only for \textit{Ureaplasma urealyticum} and/or \textit{Mycoplasma hominis} positive patients.

§Susceptible
‖Intermediate
‡Resistant

### Discussion

The most important finding of this study was that HDC-\textit{Uu} was associated with HPV infection in asymptomatic, sexually active woman at all age. Verteramo et al. suggested that \textit{Ct} and \textit{Uu} (>10^4 CCU/mL) may be risk factors for HPV infection in asymptomatic patients. Lukic et al. emphasized that \textit{Uu} (>10^4 CCU/mL) in asymptomatic woman could be a cofactor in HPV infection and may exert a negative influence on cervical cytology.

This result was also similarly observed in symptomatic woman. Pisani et al. found parallel positive rates of \textit{Uu} and HPV infection and suggested a synergistic effect between \textit{Uu} and HPV infection in CIN and cervical cancer caused by HPV.

Zhang et al. found that \textit{Uu} was the most common infection among patients with HPV, which supports our result. However, in contrast to our results, there was no significant association between \textit{Uu} and HPV infection.

Other studies suggesting a relationship between HPV infection and \textit{Uu} infection are described in table 5,3,10,12-20 These studies strongly support an association between \textit{Uu} and HPV infection. Coinfection of \textit{Uu} with HPV contributes to development of CIN. Diagnosis and treatment can be delayed in asymptomatic women, but not in symptomatic women with \textit{Uu} and HPV coinfection. Therefore, HPV testing is suggested in women with \textit{Uu} infection, regardless of symptom status.

The number of sexual partners is a known risk factor for HPV infection, Kataja et al. reported that the number of sexual partners during prior 2 years is the strongest independent risk factor for HPV infections. In our cohort, we tried to classify participants according to the number of sexual partners in the prior 2 years. Among 264 participants, 34 had 2 partners and 36 had 3 or more partners, which suggested that the cohort in our study consisted of sexually active individuals. Even after adjustment for the number of sexual partners (logistic regression analysis with cut-off at 1-2 versus 3 or more), HDC-\textit{Uu} was significantly associated with HPV infection in the present study.

Kataja et al. reported that the risk for HPV infection varied with age, being highest in the 20-29 year old group, and thereafter declining in subsequent 10-year age groups.

However, in our cohort, we found no relationship between age and HPV infection. Moreover, age was not associated with abnormal cytology or bacterial infection. Therefore, asymptomatic infection with HDC-\textit{Uu} should be eradicated, regardless of age, for the prevention of HPV infection and subsequent CIN.
Ct and Mg are known to cause STIs. According to Bhatla et al., Ct is not a direct cause of cervical neoplasia, but could be a causative factor in HPV infection.22 Several reports showed that the presence of Ct negatively affects host cell immunity against HPV, furthermore, Ct induced micro-abrasion on the cervix that can increase susceptibility to HPV.23,24 A recent study revealed that the incidence of asymptomatic Ct and Uu was 5.6% and 22.1%, respectively, whereas in this study, the incidence was 2.3% and 36.0%, respectively. However, only 2 among 6 Ct infections and 3 among 5 Mg infections had HPV infection in our study. These cases were insufficient to determine statistical significance.

In our study, the incidence of asymptomatic Uu infection was 36.0%, whereas Zhang et al. reported that the incidence of symptomatic Uu infection was 58.7%.25 The incidence rate of asymptomatic Uu infection was relatively low. However, asymptomatic Uu infection could be a cofactor in HPV infection.2 Moreover, coinfection of Uu with HPV can contribute to development of CIN. Therefore, HPV testing should be performed in women with Uu infection, regardless of symptom status.

Our research showed that, HDC-Uu, an intracellular microorganism, was related to HPV infection in asymptomatic sexually active individuals. This important finding indicates that asymptomatic subjects with potentially harmful bacteria should be treated. We should note that high risk HPV infection is the most important risk factor for cervical cancer.1 Therefore, asymptomatic infection with HDC-Uu combined with HPV should be eradicated for the prevention of CIN.

There has been persistently controversy regarding Uu as a pathogen in STIs. Therefore, it was unclear as to whether Uu colonization should be considered an infection. However, a recent meta-analysis suggested that Uu is an etiological agent in STIs.25 A recent study also demonstrated that a high density of Ureaplasma may be associated with STIs.26 When determining the clinical significance of Ureaplasma infection, the differentiation of colonization and infection is necessary because of the high prevalence in the healthy population (Ureaplasma 70-80%, Mycoplasma 30-40%). The presence of more than 10^4 CCU/mL in a sample is an additional criterion used to distinguish colonization from infection.27

Interestingly, our data also indicated that only Uu colonization with greater than 10^4 CCU/mL was significantly associated with HPV infection.

According to our results of antimicrobial susceptibility testing, Uu has a high rate of resistance to fluoroquinolones. Recently, Vargović et al. reported that 78.5% of Uu isolates were sensitive to ofloxacin, in contrast to 98.2% showing sensitivity to doxycycline.28 Susceptibilities of specific species to antimicrobial agents show regional variation according to current trends of antimicrobial use in the community.29 Our data showed that sensitivities to ofloxacin and ciprofloxacin were 40.0% and 10.5%, which were higher than the results reported by Xie et al. (sensitivities to ofloxacin and ciprofloxacin were 22.1% and 5.8%). They presented a decreasing trend of sensitivity of Uu to fluoroquinolones, and pointed out that topoisomerase IV ParE subunit plays a role in emerging fluoroquinolone resistance in Uu.30
Therefore, if Uu is detected in asymptomatic sexually active individuals in an area where susceptibility testing of Uu is not available, we recommend consideration of doxycycline or erythromycin (or its derivatives; eg, azithromycin, clarithromycin and pristinamycin) for empirical treatment.

A limitation of this study is that a partner’s past sexual history could not be clearly determined. This could represent a strong risk factor for infection with Uu and HPV. During the study, it was very difficult to complete the interview about sexual history because all the participants were asymptomatic and some of were reluctant to provide a personal history.

In conclusion, HDC-Uu (>10^4 CCU/mL) could be a risk factor for HPV infection. We recommend that women infected with Uu be treated with doxycycline or erythromycin derivatives as first line agents.

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Competing Interests

The authors have declared that no competing interest exists.

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