Ureaplasma urealyticum and *Ureaplasma parvum* in women of reproductive age

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Abstract

Objectives. To determine the incidence of *Ureaplasma urealyticum* (UU) and *Ureaplasma parvum* (UP) in symptomatic and asymptomatic women of reproductive age and to estimate antibiotic susceptibility of ureaplasma isolates.

Material and methods. This study included 424 ureaplasma positive women of 1370 tested women who visited gynecological practices during 2010. Cervicovaginal or urethral swab specimens from each patient were obtained for cultivation and molecular typing by RT-PCR.

Results. Ureaplasma spp. was identified by cultivation in 424 (34.4%) cases, of which 79.0% were from women with symptoms and 21.0% from women without symptoms. Among ureaplasma positive women, 121 (28.5%) were pregnant. Genotyping was successful in 244 strains, and the majority of samples were identified as UP (92.6%). Among genotyped isolates, there were 79.5% from symptomatic and 20.5% from asymptomatic women; 29.9% from pregnant and 70.1% from non-pregnant women. There was no difference in the incidence of ureaplasma type regarding symptoms. Antibiotic susceptibility of 424 ureaplasma isolates identified by cultivation showed that all strains were susceptible to doxycycline, josamycin, erythromycin, tetracycline, clarithromycin and pristinamicin, but there was lower susceptibility to quinolone antibiotics, i.e. 42.9% and 24.5% isolates were susceptible to ofloxacin and ciprofloxacin, respectively.

Conclusion. This study shows that UP was the most frequent isolated ureaplasma species (92.6%). Regarding antibiotic susceptibility, quinolones are not the best choice for treatment of ureaplasma infections, while macrolides and tetracyclines are still effective.

Introduction

Urogenital ureaplasma in women of childbearing age are associated with urethritis, pelvic inflammatory disease, pregnancy complications, premature birth and infertility but are also very frequent in healthy women. Mycoplasmas are the smallest known free living microorganisms of 200 to 300 nm in size. Taxonomically, mycoplasmas belong to the class of *Mollicutes* together with ureaplasma, also called T (tiny) mycoplasmas because they produce a very small colony size of only 50-60 micrometer in diameter [1]. In humans, urogenital ureaplasma infection is

caused by two species, *Ureaplasma urealyticum* (UU) and *Ureaplasma parvum* (UP), with a total of 14 serotypes. UU has characteristics of biovar T960T (or biovar 2 or A), and includes 10 large genomic serovars (0.88-1.2 Mbps): 2, 4, 5, 7, 8, 9, 10, 11, 12 and 13, while UP has characteristics of parvo biovar (or biovar 1 or B) and includes four serovars: 1, 3, 6 and 14 [2,3].

In the urogenital system UU and UP are considered pathogenic isolates. In women, the urogenital tract infection can be asymptomatic or with mild to severe symptoms, while in men ureaplasma commonly causes urethritis. If the infection spreads to the uterus or fallopian tubes in women or in the small bowel it may lead to pelvic inflammatory disease. The role of ureaplasma in pregnant women is of particular importance as the infection may lead to complications in pregnancy resulting in premature labour, miscarriage or stillborn child [2,4–9]. Undiagnosed and untreated infection can also lead to infertility. When determining the clinical significance of ureaplasma infection, the differentiation of colonization and infection is necessary because of the high prevalence of ureaplasmas in the healthy population (ureaplasma 70-80%, mycoplasmas 30-40%) [10]. The presence of more than 10^4 CFU in a sample is an additional criterion to distinguish colonization from infection.

Although considered "gold standard", culture methods could not differentiate species, UU from UP. Therefore, it is important to introduce molecular methods such as real-time polymerase chain reaction (RT-PCR), which enables distinguishing ureaplasma species [11,12]. The objectives of this study were to determine the incidence of UU and UP in symptomatic and asymptomatic women of reproductive age and to estimate antibiotic susceptibility of ureaplasma isolates.

Material and methods

Study population

The study was carried out at Gynecological Practices of Primary Health Centers in Zagreb, Croatia which are collaborating institutions of the Croatian National Institute of Public Health. Of 1370 women who visited gynaecological practices during 2010, 471 women were positive for ureaplasma isolates. Only 424 isolates were included in the analysis as for 47 isolates complete

medical records were not available. Of the total number of ureaplasma positive women 121 (28.5%) were pregnant. Women were divided in two groups, 89 (21.0%) asymptomatic women who came to the gynaecological examination because of a routine check-up, or disease conditions that were not related to urogenital system, and 335 (79.0%) symptomatic women who had at least one of the following symptoms: non-specific pain and tension in the lower abdomen, increased vaginal discharge, dispareunia, burning and frequent urination. The age of symptomatic women ranged from 16 to 64 years (mean 31.6; median 30), while the age of asymptomatic women ranged from 20 to 68 years (mean 30.7; median 30).

Specimen collection

Cervicovaginal or urethral swab specimens were collected for microbiological and molecular analysis. All specimens were obtained before antibiotic treatment. Ureaplasma cultivation was performed at the Department of Bacteriology, while the RT-PCR analysis was performed at the Department of Molecular Diagnostics of the Croatian National Institute of Public Health.

Bacterial detection and antimicrobial susceptibility

Ureaplasma identification was done by cultivation on agar and liquid medium, as well as with a commercial Mycoplasma IST 2 (BioMerieux, Marcy l'Etoile, France). The test is based on the principle of metabolic inhibition of sensitive strains. This test allows the cultivation, identification, determination of the indicative number of bacteria and determine the susceptibility of the isolates to antibiotics [13,14].

Co-infection with other microorganisms including *Gardnerella vaginalis* (GV) , beta-haemolytic Group B Streptococcus (GBS), *Candida albicans* (CA) was identified according to routine laboratory methods, including API-tests (BioMérieux SA Marcy l'Etoile, France). *Chlamydia trachomatis* (CT) identification was done with COBAS AMPLICOR CT/NG Test (Roche, Basel, Switzerland) and according to Airell et al. [15].

Real-time PCR

Two hundred eighty six samples for which the Mycoplasma IST 2 test result was $\geq 10^4$ CFU were used in subsequent identification with RT-PCR. Ureaplasma isolates were stored at -20° C until DNA isolation procedure with the commercial assays (QUIamp DNA Mini Kit; QUIAGEN

GmbH, Hilden) according to the manufacturer's instructions. Differentiating strains of UU of UP was performed as described by Mallard et al. [12].

Statistical analysis

Data and statistical analysis was performed in the Division of Molecular Medicine, Rudjer Boskovic Institute using GraphPad Prism (version 4.00) (GraphPad Software, San Diego, California, USA). Methods of descriptive statistics, Chi square ($\chi 2$)-test and Fishers exact test were used. The P-values of <0.05 were considered statistically significant.

Results

Of the 424 samples, 286 (67.4%) were analyzed by RT-PCR. In 42/286 (14.6%) samples the PCR failed to identify ureaplasma species, due to technical difficulties, while 244 samples were successfully genotyped (Table 1). There were 18 (7.4%) samples identified as UU and 226 (92.6%) as UP. Of 18 UU cases, 15 (83.3%) were isolated in symptomatic and three (16.7%) in asymptomatic women, while of 226 UP cases 179 (79.2%) and 47 (20.8%) were isolated in symptomatic and asymptomatic women, respectively. There were no statistically significant difference between the incidence of UU and UP among symptomatic and asymptomatic women ($P = 0.676$).

In the group of pregnant women, UU and UP were isolated in 4/18 (22.2%) and 69/226 (30.5%) women, respectively. In the group of women who were not pregnant, UU was isolated in 14/18 (77.8%), while UP was isolated in 157/226 (69.5%) women (Table 1). There were no statistically significant difference between the incidence of UU and UP among pregnant and non-pregnant women ($P = 0.459$).

Table 2 presents subgroups of samples including both pregnancy and symptoms data. Statistical significance (Chi – square test $P = 0.022$) was observed in UU and UP isolation in the non-pregnant subset where UU appeared more often in asymptomatic infections than UP. However, this difference is probably due to very limited number of asymptomatic infections in this subset (n=6). Using Fishers exact test, which is more suitable for small sample sizes, statistical difference was not found ($P =0.077$) . Subset of samples including only pregnant women did not indicate statistically significant difference of ureaplasma species isolation in women with or without symptoms ($P = 0.138$).

In a cohort of symptomatic women who were not pregnant, UP was found in 153 of 157 (97.5%) cases, while UU in 12 of 14 (85.7%) cases. In a cohort of asymptomatic women who were not pregnant, UP was found in 4 of 157 (2.5%) cases, while UU in 2 of 14 (14.3%) cases.

In a cohort of symptomatic pregnant women UP was found in 26 of 69 (37.7%) cases, while UU in 3 of 4 (75.0%) cases. In asymptomatic pregnant women UP was found in 43 of 69 (62.3%) cases, while UU in 1 of 4 (25.0%) cases.

In genotyped ureaplasma isolates, simultaneously associated microorganisms (Table 3) were GV (20.1%), CA (11.1%), GBS(4.1%), and CT (3.7%). However, there was no significant differences between UU and UP species in co-isolated microorganisms.

Antibiotic susceptibility of 424 ureaplasma isolates identified by cultivation (Table 4) showed that all strains were sensitive to doxycycline, josamycin, erythromycin, tetracycline, clarithromycin, and pristinamicin. Only one ureaplasma isolate showed moderate susceptibility to azithromycin. In addition, there was some resistance to quinolone antibiotics.

The antibiotic susceptibility of 244 ureaplasma genotyped by RT-PCR showed that all strains of UU and UP were sensitive to doxycycline, josamycin, erythromycin, tetracycline, clarithromycin and pristinamicin even though some isolates were resistant to quinolone antibiotics (Table 4). Lower sensitivity was observed to ofloxacin (42.9%) and ciprofloxacin (24.5%). One UU isolate (0.3%) showed moderate susceptibility to azithromycin. Regarding genotyped ureaplasma isolates, there were 72.2% UU isolates resistant to ciprofloxacin,

Discussion

In recent years urogenital ureaplasmas are highly frequent isolated in women of childebearing age. Prior to this study the prevalence of different ureaplasma species was not well studied for the Croatian population. This study showed 34.3% positive samples of urogenital tract in the female population. Zdorowska-Stefanov et al. [16] found slightly lower ureaplasma prevalence (29.8% of 541 women tested), while Kechagia et al. [17] found slightly higher prevalence (37.0% of 369 women tested). Molecular based studies have shown that most of ureaplasma isolates thus far considered UU were actually UP [18–20]. According to Kacerovský et al. [21], the prevalence of UP in a cohort of healthy women who were not pregnant was 57%, which is a

much higher prevalence than those of other genital mycoplasmas, viruses, Chlamydia or GBS infections.

In this study, most ureaplasma isolates were identified as UP (92.6%) as expected [18,21,22]. We found no significant differences between UP or UU positive individuals according to symptoms or pregnancy. There are evidence of adverse impact of ureaplasma infection on the course and outcome of pregnancy [2,4], and that ureaplasma infection in infants is associated with low birth weight and perinatal mortality [23]. Govender et al. [24] established ureaplasma high prevalence among women aged ≥ 26 years. However, association between colonization of *Mycoplasma hominis*, UU or UP and premature births was not confirmed. Results of this study showed that the UU and UP were almost equally often isolated in women who were pregnant or not (22.2%; vs. 30.5%).

Women of reproductive age often suffer from urogenital infections. In this study incidence of other concomitant bacteria and fungi with ureaplasma was investigated. Common isolated microorganisms with ureaplasma were GV (20.1%), CA (11.1%), GBS (4.1%), and CT (3.7%). The results are consistent with a study of Vogel et al. [25] who found GV the most common isolate with ureaplasma. In our study CA has been isolated in women with UP (11.9%), but no in patients with UU. Since CA causes unpleasant clinical symptoms, we believe that co-infection with CA and UP should be investigated in a large number of samples. Despite the significant role of CT infection in genitourinary tract, in our study it was found in only 3.7% of women.

In this study, the antibiotic sensitivity of ureaplasma isolates identified by cultivation showed that all strains were sensitive to doxycycline, josamycin, erythromycin, tetracycline, clarithromycin and pristinamicin, but some resistance to quinolones was observed. Limited sensitivity was observed with ofloxacin (42.9%) and ciprofloxacin (24.5%). One UU (0.3%) isolate showed moderate resistance to azithromycin. In addition, regarding the genotyped ureaplasma isolates, where 72.2% of UU isolates were resistant to ciprofloxacin, it can be concluded that quinolones are not the best choice for treatment of ureaplasma isolates. These findings are consistent with research of Baryaktar et al. [23] who estimated higher resistance to quinolones of UU, i.e. 86.2% to ofloxacin and 92.6% to ciprofloxacin. The study of Mares et al. [26] showing resistance to ofloxacin was 16.1% and 53.8% to ciprofloxacin also support the

findings in this study. However, it can be concluded that macrolides and tetracyclines are still high effective in ureaplasma infection treating.

Conclusion

In this study, both species of ureaplasma, UP and UU, appeared in women regardless of symptoms or pregnancy with UP being the predominant species in the Croatian population. Due to small number of UU samples it is so far impossible to determine differences in pathogenicity between UP and UU and further large scale studies should be done to elucidate potential differences.

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Conflict of interest

The authors have declared that no competing interests exist.

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Conclusion. This study shows that UP was the most frequent isolated ureaplasma species (92.6%). Regarding antibiotic susceptibility, quinolones are not the best choice for treatment of ureaplasma infections, while macrolides and tetracyclines are still effective.

Table 1. Ureaplasma genotypes in women according to symptoms and pregnancy status

	Ureaplasma isolates			*P* value
	U. urealyticum **(n = 18)**	***U. parvum*** **(n=226)**	**Total (n=244)**	
Symptomatic infection				
Yes	15 (83.3%)	179 (79.2%)	194 (79.5%)	0.676
No	3 (16.7%)	47 (20.8%)	50 (20.5%)	
Pregnancy				
Yes	4 (22.2%)	69 (30.5%)	73 (29.9%)	0.459
No	14 (77.8%)	157 (69.5%)	171 (70.1%)	

Table 2. Ureaplasma genotypes in pregnant and non-pregnant women

	Ureaplasma isolates			*P* value
	U. urealyticum	***U. parvum***	**Total**	
Non-pregnant women				
Symptomatic infection	12 (85.7%)	153 (97.5%)	165(96.5%)	0.077*
Asymptomatic infection	2 (14.3%)	4 (2.5%)	6 (3.5%)	
Subtotal	14	157	171	
Pregnant women				
Symptomatic infection	3 (75.0%)	26 (37.7%)	29 (39.7%)	0.138
Asymptomatic infection	1 (25.0%)	43 (62.3%)	44 (60.3%)	
Subtotal	4	69	73	

* Fishers exact test

Table 3. Microorganisms associated with *U. parvum* and *U. urealyticum*

Microorganisms	Ureaplasma isolates			
	U. urealyticum **(n = 18)**	***U. parvum*** **(n=226)**	**Total (n=244)**	***P*** **value**
G. vaginalis	3 (16.7)	46 (20.4)	49 (20.1)	0.707
C. albicans	0	27 (11.9)	27 (11.1)	0.119
GBS	1 (5.6)	9 (4.0)	10 (4.1)	0.746
C. trachomatis	1 (5.6)	8 (3.5)	9 (3.7)	0.662
Other microorganisms*	12 (66.6)	142 (62.8)	154 (63.1)	0.746

*microorganisms isolated in small numbers and urogenital physiological flora

Table 4. Antimicrobial susceptibility of the total isolated ureaplasma and of specific genotype

Antimicrobial agent	Ureaplasma isolates (N=424)			Ureplasma urealyticum (N=18)			Ureaplasma parvum (N=226)		
	S	I	R	S	I	R	S	I	R
Doxycycline	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0
Josamycin	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0
Ofloxacin	182 (42.9%)	220 (51.9%)	22 (5.2%)	5 (27.8%)	12 (66.7%)	1 (5.5%)	94 (41.6%)	122 (54.0 %)	10 (4.4%)
Erythromycin	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0
Tetracycline	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0
Ciprofloxacyn	104 (24.5%)	170 (40.1%)	150 (35.4%)	2 (11.1%)	3 (16.7%)	13 (72.2%)	40 (17.7%)	107 (47.3 %)	79 (35.0%)
Azithromycin	423 (99.7%)	1 (0.3%)	0	17 (99.9%)	1 (0.1%)	0	226 (100%)	0	0
Clarithromycin	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0
Pristinamicin	424 (100%)	0	0	18 (100%)	0	0	226 (100%)	0	0

S, susceptible, I, intermediate, R resistant