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Urogenital Mycoplasmosis and Pregnancy

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Abstract

Urogenital mycoplasmas *Ureaplasma urealyticum, Ureaplasma parvum* and *Mycoplasma hominis* have long been considered commensals of human urogenital microflora. Several studies have recently clarified whether these bacteria could cause or be associated with various obstetric complications. Epidemiologic studies have found high prevalence of Ureaplasma spp. and M. hominis among otherwise healthy population. On the other hand, *U. urealyticum, U. parvum* and *M. hominis* have increasingly been linked to adverse pregnancy outcomes such as spontaneous pre-term labor, pre-term premature rupture of fetal membranes, miscarriage, stillbirth and low birth weight. However, no convincing causal relationship has been shown. Studies have shown that antibiotics resistance is on the rise and differs considerably by regions. Screening of asymptomatic patients for *M. hominis*, *U. urealyticum* and *U. parvum* is currently still not indicated.

Keywords: Mycoplasmas; Pregnancy; *M. hominis*; Ureaplasmas

Introduction

The name mycoplasma has been used as the general name for the class *Mollicutes* the smallest free-living microorganisms. In the urogenital tract, the relevant *Mollicutes* are *Mycoplasma genitalium* and *Mycoplasma hominis* and two species of ureaplasmas- *Ureaplasma urealyticum* and *Ureaplasma parvum*. This article aims to give a short overview of associations and causative roles of aforementioned mycoplasmas with various obstetric complications. Brief summary is provided about recent trends in treatment.

Epidemiology

Ureaplasmas and *M. hominis* are considered opportunistic pathogens because they can be isolated from the lower urogenital tract of healthy women as well as from individuals with disease. Table 1 summarizes the prevalence of urogenital mycoplasmas as found by different researchers.

As can be seen from Table 1, then prevalence varies considerably from study to study [1-5]. Prevalence of *M. genitalium* has been found to be between 0.3-1.2% [6,7].

That is lower than the prevalence of *Chlamydia trachomatis* but higher than that of *Neisseria gonorrhoeae.* A few researches have differentiated between *U. urealyticum* and *U. parvum*. In these studies *U. parvum* makes up around 80% of total detected *Ureaplasma spp*. Some studies have found *M. hominis* only as co-infection with ureaplasmas [6,8,9].

Role in obstetric complications

Ureaplasmas and *M. hominis* are considered commensals of human microflora, although increasing amount of research finds associations between adverse outcomes of pregnancy and colonisation of ureaplasmas and *M. hominis*. Nevertheless, there is still no definitive consensus on their causative role. Next, short summary of recent findings is provided.

Study	*Ureaplasma spp*	*U. parvum*	*M. hominis*	*M. Genitalium*	Sample size	Population
Pignanelli et al.	-	-	3.30%	-	2,480	Symptomatic patients in Italy
Verteramo et al.	28%	-	5%	-	3,155	Non-pregnant women aged 14-57, routine gynaecological care, in Italy
Pónyai et al.	12%	-	1.3%	-	2,309	Sexually active women in Hungary
De Francesco et al.	18%	-	2%	-	9,956	Outpatients, routine check, pregnancy screenings etc, Italy

Ouzounova-Raykova et al.	15%	-	3%	0.3%	348	Women in Bulgaria
Tibaldi et al.	17%	-	2%	-	27,000	Non-pregnant women
Zdrodowska-Stefanow et al.	23%	-	4%	-	541	Women aged 18-55, gynaecological and STD outpatient clinics
Naaber et al.	7.7% Uu*	32%	8%	1.2%	4,985	85% women, 15% men, Estonian STD clinics patients
Ye et al.	53%	-	12%	-	37,055	Women in Hangzhou
Redelinghuys et al.	76%	-	40%	-	96	Pregnant South-African women
Kataoka et al.	8.7% Uu*	52%	11%	0.8%	877	Pregnant women
*Uu-*Ureaplasma urealyticum*						

Table 1: Prevalence of urogenital mycoplasmas.

Ureaplasma spp.

Ureaplasma genital tract colonization has been associated with adverse pregnancy outcomes such as spontaneous abortion [10], premature rupture of membranes (PROM) [4], premature delivery [11], neonatal morbidity and perinatal death [12]. The methodology and samples vary considerably between studies, which makes combining and synthesizing the result difficult. Therefore, the results are presented as stated by studies in a Table 2.

Study	Sample size	Population	Result
Witt et al.	132	Patients with preterm labor or PROM, sample from amniotic cavity	Statistically significant association between intrauterine colonization with *U. urealyticum* and both therapy-resistant preterm labor and preterm premature rupture of membranes (PPROM) (p<0.001)
	75	Control group, other indication for cesarean section	
Kacerovský et al.	225	Patients with PROM, 24 to 36 weeks of gestation	Statistically significant difference between groups with PPROM and control group (p<0.0001).
	225	Pregnant control group	
Ahmadi et al.	109	Spontaneous abortion, 10 to 20 weeks of gestation	Statistically significant association between *U. urealyticum* endocervical infection and spontaneous abortion at gestation age between 10-20 weeks
	109	Pregnant control group	
Abele-Horn et al.	172	*U. urealyticum* positive pregnant women	Statistically significant association between vaginal colonisation with *U. Urealyticum* and decrease of birth weight (p<0.0001), gestational age (p<0.0001), increase of chorioamnionitis (p<0.0001) and preterm delivery (p<0.001). Low colonization levels had no effect on an adverse outcome of pregnancy
	123	*U. urealyticum* negative pregnant women	
Mitsunari et al.	23	Patients with preterm labor	Statistically significant association between cervical *U. Urealyticum* colonization and preterm delivery (p=0.0111)
	59	Pregnant control group	
Kataoka et al.	21	Patients with preterm labor or abortion	Vaginal colonization with *U. parvum*, but not *U. urealyticum,* is associated with late abortion or early preterm birth
	856	Pregnant control group	

Table 2: Results of studies on association of ureaplasmas with obstetric complications.

Witt et al. [13] found that the amniotic cavity of 44% of patients with PROM and therapy-resistant preterm labor was colonized with *U. urealyticum* compared to only 2.7% in control group of pregnant women. Mitsunari et al. [11] findings support the association between cervical *U. urealyticum* and preterm delivery (controls colonisation 46% compared to 87% in preterm delivery patients).

Very few studies distinguish between *U. urealyticum* and *U. parvum* and describe the influence of *Ureaplasma spp.* combined. Even if an

article states that *U. ureaplasma* is studied, then careful examination of methods section reveals that the method used does not allow to differentiate between biovars. Nevertheless, some researchers have made the distinction. Kataoka et al. [14] found that *U. parvum* but not *U. urealyticum* is associated with late abortion or early preterm birth. Kasprzykowska et al. [15] found that colonization of the lower urogenital tract with *U. parvum* can cause asymptomatic infection of the upper reproductive system. Kasper et al. [16] found that the increased amount of *U. parvum* was significantly linked to histological chorioamnionitis, PROM together with preterm labor, early-onset sepsis, and bronchopulmonary dysplasia. Furthermore, no significant difference between the bacterial load of *U. urealyticum* and neonatal outcome was observed [16]. The importance of bacterial load was found by Abele-Horn et al. [17]. The study revealed that high colonization (>10^5 cfu/ml) level with *U. urealyticum* was associated with a significant increase of clinical chorioamnionitis, PROM and preterm delivery. Low density vaginal colonization levels had no effect on clinical chorioamnionitis and preterm delivery [17].

Greenow et al. [18] studied whether treatment of pregnant women heavily colonized with ureaplasma with erythromycin could have an impact on birth weight, but found no statistically significant difference [18]. However, in this study the antibiotics treatment was started only between 22-32th week of gestation, whereas obstetric adverse outcomes, such as abortion may arise much earlier.

M. hominis

Evidence has accumulated that *M. hominis* may be of significance in the condition of bacterial vaginosis. Bacterial vaginosis (BV) in turn has been associated with subsequent early pregnancy loss [19]. Donders et al. [19] studied BV and found that *M. hominis*, and *U. urealyticum* were associated with an increased risk of early miscarriage. *M. hominis* may act symbiotically with other BV-associated bacteria or as the sole pathogen based on the observation that this mycoplasma can be found in large numbers in the vagina of most women with BV, but less often in healthy women [20].

M. genitalium

Mycoplasma genitalium is a globally important sexually transmitted pathogen known to cause urethritis [21]. However, there is no conclusive evidence supporting its role in adverse obstetric outcomes and tubal infertility. Data suggests an association between cervicitis and *M. genitalium*. Supporting evidence of causal relationship between pelvic inflammatory disease and *M. genitalium* is moderate to strong [21].

Existing data provide some support for the hypothesis that *M. genitalium* can cause female infertility, but are inconclusive [22]. A few studies have found an independent association between vaginal presence of *M. genitalium* and preterm delivery [23,24]. However, causative association of *M. genitalium* with adverse obstetric outcomes remains unestablished [25].

Diagnostics

Ureaplasmas and *M. hominis* are considered to be a part of natural microflora among healthy women and men. Consequently, the detection of these bacteria has a low positive predictive value in relation to diseases. Therefore, currently, most reviews do not recommend the inclusion of these pathogens into the routine sexually transmitted infections (STI) screening protocols and state that asymptomatic individuals should not be screened with culture or nucleic acid amplification tests (NAAT).

As previously discussed, detection of *M. genitalium* is strongly correlated to diseases. As it is detected only rarely in healthy individuals, the positive predictive value of the test for *M. genitalium* is high. It has been suggested that *M. genitalium* could be among routinely screened microbes as are *C. trachomatis* and *N. gonorrhoeae*.

Laboratory Methods

Culture and microscopy

Culture has been previously considered the gold standard in the detection of ureaplasmas but it is a difficult method since these fastidious organisms require the presence of serum, metabolic substrate and growth factors [26]. In addition, some commercial kits available for diagnosis of urogenital mollicute infections have demonstrated lack of diagnostic sensitivity [27]. Lack of a rigid cell wall makes it nearly impossible to directly visualize ureaplasma by light microscopy. The laboratory testing of *M. genitalium* has been particularly difficult as it takes several weeks or even months for each isolate to grow, making culture impossible to use for diagnostics in routine clinical practice [28].

Therefore, owing to the poor and extremely slow growth of the bacterium in culture, diagnosis of *M. genitalium* infection is performed exclusively using nucleic acid amplification tests (NAAT) [28].

Polymerase chain reaction (PCR)

PCR has been introduced in the practice because of the possibility to use different clinical materials, quick test results and possibility to detect different pathogens in a swab [7]. PCR is also more sensitive than culture for detection (<100 genome copies) of nonviable as well as viable ureaplasmas. The results of PCR are available in a day, whereas a culture takes 2-5 days. The most commonly used gel-based traditional and real-time PCR protocols target the common multiple-banded antigen (mba), urease or 16s RNA genes. Currently new sensitive and low-cost multiplex PCR methods are being developed to make diagnosis by nucleic acid amplification tests (NAATs) more cost-efficient [29].

However, at the moment there is no gold standard PCR test which to compare other new tests with. When choosing the PCR test for use, it must be accounted for that PCR of some MgPa-related sequences may fail to detect some strains of *M. genitalium* due to antigenic variability [25,28].

Quantitative-PCR (qPCR)

Conventional PCR is restricted in the accurate quantification of microorganisms. In contrast, quantitative real-time PCR (qPCR) using fluorescence dyes or probes facilitate the quantification of amplified viral, bacterial, and parasitic products. As it was previously discussed, in some obstetric complications the amount of bacteria is more important than the mere presence of it [16].

PCR is an excellent alternative to culture, but culture allows antibiotic susceptibility testing. However, molecular testing for macrolide and fluoroquinolone resistance mediating mutations is also possible.

Specimen collection

There is still no consensus as to which specimens have the best sensitivity in detection of ureaplasmas and *M. genitalium*. For *M. genitalium* the use of more than one specimen may significantly improve the diagnostic sensitivity. Lillis et al. [30] found that the single best specimen for the detection of *M. genitalium* infection was vaginal swab specimen, followed in order of decreasing relative sensitivity by endocervical swab specimen (74.3%), urine specimen (61.4%), and rectal swab specimen (24.3%).

Vaginal swab combined with endocervical swab provided a sensitivity of 95.7% [30]. Research has also shown that self-collected vaginal swabs are equal to clinician-collected vaginal swabs for diagnosis of *C. trachomatis* and *N. gonorrhoeae*, and there is no reason to doubt that the same would be true for *M. genitalium* [30].

General Treatment

Mycoplasmas and ureaplasmas lack a cell wall, the target of beta-lactam antibiotics and vancomycin, which makes them resistant to these antibiotics. Additionally, ureaplasma species have natural resistance to lincosamides (e.g. clindamycin) and *M. hominis* possesses inherent resistance to macrolides, except josamycin [31].

Historically, tetracyclines, macrolides, and quinolones have been the major antibiotics used in the treatment of urogenital infections caused by mycoplasmas. However, their therapeutic efficacy may be unpredictable due to increasing resistance. The extent of resistance varies regionally according to different antimicrobial therapy policies and the history of prior antimicrobial exposure in different populations. Recently, several articles have been published that study the resistance of *M. hominis* and ureaplasma to antibiotics. Table 3 summarizes the results of these studies. De Francesco et al. [32] studied a sample of 9,956 patients in Italy. Both *M. hominis* and *Ureaplasma spp.* (no differentiation was made between *U. parvum* and *U. urealyticum*) were most sensitive to doxycycline and tetracycline, as well as to josamycin.

Clarithromycin and josamycin were the most potent macrolides against ureaplasmas. The only macrolide effective against *M. hominis* was josamycin. Another antibiotic effective against both microbes was pristinamycin. Other two macrolides that were studied-azithromycin and erythromycin - were only moderately effective [32]. Resistance to erythromycin has been reported additionally by Ponyai et al. [31] and Krausse et al. [33] who determined that the resistance of ureaplasmas to erythromycin is 81% and 21%, respectively.

	Francesco et al. (9,956)		Ponyai et al., (2,309)		Krausse et al., (469)		Ye et al. (37,055)		Pignanelly et al. (2,480)
	Ureapl.	*M. hominis*	*Ureapl.*	*M. hominis*	*Ureapl.*	*M. hominis*	*Ureapl.*	*M. hominis*	*M. hominis*
Doxycycline	2%	1%	2%	2%	1%	10%	2%	0%	4%
Tetracycline	2%	1%	4%	12%	3%	11%	3%	2%	7%
Erythromycin	10%	99%	81%	-	21%	96%	1%	98%	85%
Clarithromycin	5%	99%	-	-	5%	99%	0%	97%	80%
Josamycin	1%	1%	-	-	2%	3%	0%	0%	1%
Azithromycin	5%	99%	10%	-	7%	99%	0%	67%	75%
Ciprofloxacin	60%	100%	-	-	16%	8%	75%	55%	60%
Ofloxacin	5%	100%	25%	5%	2%	2%	53%	55%	22%
Pristinamycin	1%	1%	-	-	-	-	0%	0%	4%
Clindamycin	-	-	75%	5%	43%	0%	-	-	-

Table 3: Percentage of resistant strains, sample size in brackets.

Pignanelly et al. [5] studied *M. hominis* and found that the isolates were sensitive to tetracycline and doxycycline but resistant to fluoroquinolones and macrolides except jocamycin. Krausse et al. [33] found that doxycycline was the most active tetracycline against ureaplasmas and *M. hominis*. However, 10-13% of *M. hominis* was resistant to tetracyclines [33].

Nevertheless, doxycycline is still the drug of choice for the treatment of urogenital mycoplasma infections and may also be used for co-infection with *M. hominis* [33]. However, resistant strains are increasingly prevalent. In accordance with current guidelines, the International Union against Sexually Transmitted Infections (IUSTI) recommends use of macrolides in case of uncomplicated *M. genitalium* in the absence of macrolide resistancy mediating mutations: azithromycin 500 mg on day one, then 250 mg once daily for days 2-5 orally or josamycin 500 mg 3 times daily for 10 days.

If case of macrolide-resistancy, moxifloxacin 400 mg once daily for 7-10 days may be considered as a treatment option, however it is contraindicated in pregnancy [25,34]. Josamycin has been shown to be *in vitro* effective against *M. genitalium* [35]. This 16-membered macrolide is widely used in Italy, Russia, France, Spain, etc.

In recently published study treatment with josamycin was associated with 93.5% eradication rate in male patients with *M. genitalium* infection with josamycin 500 mg three times daily for 10 days [36]. In countries where josamycin is available, it could be considered for treatment in case of *M. genitalium* infection.

Treatment during pregnancy

During pregnancy, the list of antibiotics that are not contraindicated but effective against urogenital mycoplasmas is much shorter. Macrolides and clindamycin are allowed. Erythromycin, the antibiotic most commonly used for treating pregnant women, has shown only moderate activity. The only macrolide that has shown consistent effectiveness against both ureaplasmas and *M. hominis* is josamycin which is also allowed to be used during pregnancy [27,32,37,38]. The different configuration of the molecule of josamycin makes it resistant to efflux pump, an important mechanisms of resistance that bacteria may possess [39,40]. *M. genitalium* infections can be treated with azithromycin and josamycin, however, resistance may pose a problem.

Conclusion

M. hominis and *U. urealyticum* may be part of the normal vaginal flora but both are associated with obstetrics complications. The question of who should be screened for urogenital mycoplasmas and whether to treat the colonization to prevent obstetrics complications remains currently unsettled. *M. genitalium* is a definite urogenital pathogen and needs treatment. In accordance with current guidelines, josamycin and azithromycin are treatment of choice in case of the absence of macrolide resistance associated mutations in *M.genitalium*. Josamycin is safe to use in pregnancy in case there is a need to treat urogenital mycoplasmosis.

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