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UREAPLASMA UREALYTICUM, MYCOPLASMA HOMINIS AND ADVERSE PREGNANCY OUTCOMES

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ABSTRACT

Purpose of review:

Mycoplasma hominis and *Ureaplasma urealyticum* may colonize the human genital tract and have been associated with adverse pregnancy outcomes. Chorioamnionitis, spontaneous preterm labour and preterm premature rupture of membranes are significant contributors to neonatal morbidity and mortality. However, since these bacteria can reside in the normal vaginal flora, there are controversies regarding their true role during pregnancy and thus the need to treat these organisms.

Recent findings:

We review here the recent data concerning mycoplasmas epidemiology and their clinical role during pregnancy. The association of these organisms with preterm labour has been suggested by many observational studies, but proof of causality remains limited. Polymerase chain reaction is an excellent alternative to culture to detect the presence of these organisms, but culture allows antibiotic susceptibility testing. Whether antimicrobial treatment of mycoplasma-colonised pregnant patients can effectively reduce the incidence of adverse pregnancy outcomes warrants further investigations.

Summary:

The role of *Mycoplasma spp.* and *Ureaplasma urealyticum* in adverse pregnancy outcomes is increasingly accepted. However, sole presence of these microorganisms in the vaginal flora

might be insufficient to cause pathological issues, but their combination with other factors such as bacterial vaginosis or cervical incompetence are needed to induce preterm birth.

Keywords:

Mycoplasma Ureaplasma, neonatal infections, chorioamnionitis, preterm premature rupture of fetal membranes (PPROM), prematurity

INTRODUCTION

Adverse pregnancy outcomes that include miscarriage, stillbirth and preterm labour are a major clinical concern for obstetricians and neonatologists. Miscarriage and stillbirth are defined as the spontaneous termination of pregnancy before and after 20 weeks of gestation respectively [1]. Chorioamnionitis is an acute infection of the placental membranes, and includes both the clinical intrauterine infection and/or the histological processes [2]. Preterm labor (PTL) occurs before 37 weeks gestation and is defined as uterine contractions that lead to shortening of the cervix. All these conditions could be occasionally caused by genital mycoplasma.

Over 200 different species of *Mycoplasma* and *Ureaplasma* have been identified to date in animals, arthropods and plants [3, 4]. In humans, these species are now known to be located primarily in the respiratory or urogenital tracts. *Mycoplasma* was first isolated from a Bartholin's gland abscess in 1937[5]. However, the term *Mycoplasma* was only introduced in the 1950's and it originates from the Greek "fungus" (*mykes*) and "formed" (*plasma*). *Ureaplasma* was cultured *in vitro* for the first time in 1954, after being isolated from urethras of men presenting with nongonococcal urethritis [6]. In the 1960's, these organisms were found to be unable to produce peptidoglycans and cell wall components, making them unique among the prokaryotes. Lacking a rigid cell wall make *Mycoplasma* osmotically fragile, resistant to β-lactam antibiotics and prevents Gram staining. Due to their small genomes and their limited biosynthetic abilities, these fastidious microorganisms require complex growth media (with sterol and serum), which limited our understanding of their ecology and pathogenesis. However, during the last ten years, new molecular methods have significantly increased our understanding of their epidemiology and pathogenic potential.

Historically, *Mycoplasma hominis* and *Ureaplasma urealyticum* have been the subject of many studies, especially on their role in infections of the genital tract. A growing body of evidence suggest an association of *Mycoplasma* and *Ureaplasma* with adverse pregnancy outcomes, including infertility, miscarriage, stillbirth, PTL, postpartum endometritis, as well as chorioamnionitis. Moreover, neonates might develop *Mycoplasma* and *Ureaplasma* related lung diseases, bacteremia and meningitis. On the other hand, these bacteria can also be part of the normal genital flora, which raised controversies concerning their role in adverse pregnancy outcomes.

In the present paper, we aim to review recent data that link these 2 microorganisms with the above mentioned adverse pregnancy outcomes. This review should benefit both infectious disease specialists and obstetricians in the understanding of pathological outcomes related to mycoplasma during pregnancy. Neonatal infections, *Mycoplasma*-related ectopic pregnancies or post-partum endometritis are reviewed elsewhere [3, 4, 7-9].

EPIDEMIOLOGY

Ureaplasma urealyticum and *Mycoplasma hominis* are often identified simultaneously in women's the vulvovaginal flora [10, 11], therefore, the term "genital mycoplasmas" is often used in the literature to refer to both species. Genital mycoplasmas can be detected in 67%, 40%, and 25% of sexually active, sexually inactive and postmenopausal women, respectively [12]. Colonization during pregnancy with *U. urealyticum* and *M. hominis* varies between 35-90% and 5-75%, respectively [13, 14]. The prevalence of these microorganisms has been significantly associated with low socioeconomic status, ethnicity, hormonal changes (pregnancy, menopause) and high number of sexual partners. [4, 10, 15]. Consequently, when studying the prevalence of these bacteria in women, all these co-variables or confounding factors should be considered, since they largely explain the variation in prevalence between different studies (Table 1A&B).

UREAPLASMA, *MYCOPLASMA* & ADVERSE PREGNANCY OUTCOMES

A direct causal relationship between *U. urealyticum* and *M. hominis* and adverse pregnancy outcomes is difficult to demonstrate, due to the polymicrobial colonization of the genital tract and high prevalence of colonization. The precise significance of *U. urealyticum* and *M. hominis* in bacterial vaginosis thus remains debatable [3, 16, 17].

Growing experimental evidence of adverse pregnancy outcomes has been accumulated using different animal models (reviewed in [16]). Moreover, *Mycoplasma* are the most common microorganisms isolated from amniotic fluid, cord blood, respiratory tract and cerebrospinal fluid of infants born prematurely who develop bronchopulmonary dysplasia and developmental disabilities [12, 16].

Table 1A summarizes human studies examining *Ureaplasma* in pregnancy and their relationship with adverse pregnancy outcomes (including PTL, premature preterm rupture of membranes [PPROM] and chorioamnionitis). In uncomplicated pregnancies ("Controls" in Table 1A), colonization with *U. urealyticum* ranged from 2.7% to 70%. Huge variations in colonization rates with this organism were observed between studies. Conflicting results in the literature may be attributed to the following factors: 1) study design (prospective or retrospective); 2) gestational age at study entry (1^{st} or 2^{nd} trimester or at symptoms occurrence); 3) outcome studied (preterm labor with or without preterm birth); 4) site of sample collection (vagina, amniotic fluid or placenta); 5) diagnostic method used (culture and/or PCR; specificity of the test at species level); 6) target other pathogens (bacterial vaginosis). Among 22 studies comparing adverse pregnancy outcomes with a control group of uneventful pregnancies, 15 showed a significant association with the presence of *U. urealyticum* (Table 1A). Most of these studies were based on cervico-vaginal samples (n=17/22) and culture methods (n=16/22). A significant association between *Ureaplasma* and adverse pregnancy outcomes was found more frequently when culture was used (n=12/16) rather than PCR (n=3/6), which may reflect publication bias. Among the 5 studies based on amniotic fluid samples, all but one small study (n=40) [18] demonstrate a significant association between *Ureaplasma* and adverse pregnancy outcomes.

Regarding *Mycoplasma hominis*, a significant association with adverse pregnancy outcome was found in 6 out of 11 studies (Table 1B). Most of these studies were based on cervico-vaginal samples (n=8). It is noteworthy that all the studies based on amniotic fluid samples showed a significant association between *M. hominis* and adverse pregnancy outcomes.

Studies published during the last 3 years add significant support to the role of urogenital mycoplasmas in adverse pregnancy outcome. Choi *et al.* [11] detected *U. urealyticum* and *M.*

hominis in 62.7% and 12.7% of pregnant patients with symptoms of PTL, respectively. Despite a higher observed prevalence in the subgroup of patients who ultimately delivered preterm, statistical significance was not reached.

A recent large prospective observational study [19] of cervical swabs obtained at the first prenatal visit found a significant correlation between preterm delivery and *Ureaplasma* colonization (odds ratio (OR) 1.64; 95% confidence interval (CI) 1.08-2.48; p = 0.02). The authors used multiple logistic regression analysis to control for known risk factors for preterm birth and the presence of other pathogenic microorganisms.

Bayraktar *et al.* [10] found that 54% of patients were positive for *U. urealyticum* and/or *M. hominis* in the symptomatic group, whereas only 4% were positive for these organisms in the control group ($p<0.05$). The presence of these bacteria was also significantly correlated with low birth weight and early gestational age. However, the low prevalence of mycoplasma in the uneventful pregnancy group may reflect a bias in the number of sexual partners and exposure to other pathogens.

Kacerovsky *et al.* [20, 21] recently published 2 reports investigating the presence of mycoplasma in amniotic fluids of pregnancies complicated by PPROM. Chorioamnionitis was associated with a higher bacterial load of genital mycoplasmas [20]. Moreover, the intensity of the intra-amniotic inflammatory response to genital mycoplasmas was inversely related to gestational age [21]. This may explain the increased rate of adverse pregnancy outcomes and vertical transmission of mycoplasmas in very preterm or low birth weight neonates [22, 23]. In addition, intraamniotic and maternal inflammatory responses were more severe with mycoplasma than with other microorganisms in patients with PPROM [24]. Finally, *Ureaplasma* was isolated from 63 out of 151 placentas from preterm delivered infants (<32 weeks of gestation) [25]. Evidence of

chorioamnionitis was identified in 83% of the *Ureaplasma*-positive placentas and only in 30% of the *Ureaplasma*-negative ones ($p<0.01$). *Ureaplasma*-colonization was therefore an independent risk factor for chorioamnionitis (OR 11; 95%CI 5-25) [25].

DIAGNOSIS

Advantages and limitations of serology, culture and molecular methods for the diagnosis of mycoplasma infections have recently been reviewed by Waites *et al*. [26]. Here, we focus on diagnostic methods of *Ureaplasma urealyticum* and *Mycoplasma hominis* during pregnancy.

Serology

To our knowledge, there are no serological assays for genital mycoplasma that have been standardized and made commercially available. Thus, serological tests have been primarily developed and used in research settings.

Culture

The gold standard for detection of *Mycoplasma hominis and Ureaplasma spp*. remains culture. These bacteria may be isolated from vaginal secretions, amniotic fluid, placental tissue and cord blood during pregnancy. Culture has a major advantage in that it provides isolates for antimicrobial susceptibility testing. Appropriate techniques and media are needed to perform cultures of these organisms (Figure 1). Several limitations to the broad use of culture include susceptibility to drying, need for specific expensive media, 2-5 days laboratory procedures and technical expertise. Moreover, definitive species identification may require additional investigations such as PCR assay [4, 26], also some commercial growth media allow differentiation between *U. urealyticum* and *M. hominis* (Figure 1c).

PCR

Several PCR diagnostic protocols for detection of *M. hominis and U. urealyticum* are available, which target urease, 16S rRNA or the multiple-banded antigen (mab) gene [26-28]. Moreover, species and serovar-specific primers are available [26-28]. PCR has several advantages when compared to other diagnostic tools: (1) no viable organisms are needed (positivity even after antibiotic treatment), (2) the limit of detection is lower than in culture, and (3) results are available in less than 24 hours. Table 3 shows the detection rate of culture and PCR methods in studies performed during pregnancy. All but one study [11] show better sensitivity with PCR compared to culture [29, 76, 77]. Oh *et al.* found that culture of amniotic fluid alone would have missed 91% of genital *Mycoplasma* [29].

Conventional PCR, real-time PCR (for detection and quantification), nested-PCR (re-amplification with a second set of primers) and multiplex PCR have all been used for genital mycoplasma detection. In year 2010, *Xiao et al.* [27] compared culture with conventional PCR and a new species-specific multiplex real-time PCR. Real time PCR detected 15.2% more positive samples than did culture (24.2% versus 39.4%). Among *Ureaplasma*-positive cultures, multiplex real-time PCR assay reduced false-negative results from 9.3% to 3.1% compared to traditional PCR.

Others have also developed tools for the simultaneous detection of multiple genital pathogens, such as *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, Mycoplasmas, Treponema pallidum,* and *herpes simplex virus* type 1 and 2 in urogenital specimens[30, 31]. Finally, novel rapid DNA microarray assays enable identification of up to 37 *Mycoplasma* species from single and multiple infections in a single run [32].

TREATMENT DURING PREGNANCY

Antimicrobial susceptibility of *Ureaplasma* and *Mycoplasma*

Antimicrobial susceptibility of *Ureaplasma* and *Mycoplasma* isolated during pregnancy are shown in table 2, where data were compiled from the recent studies [4, 10, 11, 33, 34]. Since *Mycoplasma* and *Ureaplasma* lack peptidoglycan, they are naturally resistant to beta-lactams. Sulfonamides or trimethoprim are also inefficient against these bacteria due to the absence of folic acid synthesis. *Mycoplasma* spp. are generally considered susceptible to tetracyclines, fluroquinolones, macrolides and clindamycin; about 10% and 40% of *Ureaplasma* and *Mycoplasma* spp. are resistant to tetracyclins, with potential cross-resistance to erythromycin. As proposed by others [3, 35], clindamycin may represent a potential safe treatment during pregnancy for *Ureaplasma* and *Mycoplasma* spp. resistant to macrolides, since tetracyclines are contraindicated.

In recent studies investigating strains isolated during pregnancy [10, 11], antimicrobial susceptibility of *U. urealyticum* was different from that of *M. hominis*: *U. urealyticum* was more sensitive to macrolides whereas *M. hominis* was more sensitive to quinolones, congruent with known MCI (table 2) [90].

Only few studies investigated maternal and transplacental pharmacokinetics of different antibiotics [36, 37]. Azithromycin has a rapid serum half-life in gravid women with a prolonged half-life and high-sustained antibiotic levels noted within myometrium and placental tissue. However, Heikkinen *et al*.[37] reported that the transfer of erythromycin and azithromycin across the human placenta were only 3.0% and 2.6%, respectively. Some authors reinforce the urgent need to study maternal and transplacental pharmacokinetics and placental transfer antibiotic regimens efficient on mycoplama [16]. Based on clinical studies, azythromycin

appears to be an excellent treatment for both genital mycoplasma. Indeed, similar *U. urealyticum* eradication rates (>90%) were obtained with azythromycin 1g single dose versus doxycycline for 7 days [89].

Antimicrobials to prevent adverse pregnancy outcomes in patients colonized with *Ureaplasma* and *Mycoplasma*

It is difficult to make specific recommendations for genital mycoplasma infections treatment in pregnant women, because very few clinical studies address *in vivo* efficacy of antibiotics. Experimental animal model studies showed that specific maternal antibiotic therapy can eradicate *Ureaplasma* from amniotic fluid, placenta and fetus, with subsequent prolongation of pregnancy and less severe neonatal injuries [38].

Although there are reports of maternally administered antibiotics for eradication of mycoplasma intra-amniotic infection, there is little agreement in the literature regarding their effectiveness in preventing adverse pregnancy and neonatal outcomes [34, 39-43].

In one study [42], second trimester amniocentesis samples were cultured for *U. urealyticum*, and positive cultures were found in 44 out of 2,718 cases (1.6%). Thirty-five culture-positive patients were treated with oral erythromycin. The rates of second trimester spontaneous abortion was 11.4% and 44.4% in treated and untreated patients, respectively, while the rate of preterm delivery was similar between the two groups (19.4 and 20%). This work suggest the effectiveness of erythromycin on *U. urealyticum* fetal infection. However, other pathologic agents related to miscarriage, such as *Waddlia chondrophila [44-47]* not tested in this work and susceptible to erythromycin[48] may act as confounding factors. Other case reports gave similar

results: Romero *et al.* [39] and Mazor *et al.* [41] both reported that *U. urealyticum* was eradicated from the amniotic fluid of 2 patients after a course of antibiotic treatment which included erythromycin for 6-10 days.

In 2011, the Cochrane database identified only one eligible randomized control trial investigating antibiotic use in pregnant women colonized with either *U. urealyticum* or *M. hominis[49]*. In this study, colonized pregnant women were treated with erythromycin or clindamycin (n=644) versus placebo (n=427) between 22-32 weeks of gestation. There was no data to assess the effectiveness of antibiotics in reducing the incidence of premature birth. The rate of low birthweight (under 2500g) was not statistically different between groups. Of note, over 50% of women were excluded from the analysis due to poor adherence to the study protocol.

In conclusion, the indications for treatment, the choice of medication (or antibiotic), the dosage and the duration remain to be further studied and defined. Based on this review, we propose to treat *U. urealyticum* using macrolides as first-line treatment and clindamycin as second-line. For M. hominis that is generally resistant to macrolides, clindamycin represent the first choice given the relative contraindication of doxycicline and quinolones during pregnancy.

CONCLUSION

We reviewed here the literature regarding *Mycoplasma* and *Ureaplasma* with an emphasis on the last two years. Growing evidences suggest a role of these microorganisms in adverse pregnancy outcomes. For diagnosis, culture is still the gold standard, but molecular methods are useful complementary tools. The treatment during pregnancy is still debated, mainly concerning prevention of preterm labour. Analysis of the whole vaginal microbioma is needed to define the specific role of *Mycoplasma* and *Ureaplasma* in combination to the other microorganisms during pregnancy. Indeed, study of the vaginal microbiota and its natural dynamics in healthy pregnant women and women suffering from PTL may give new answers for the very limited understanding of the etiology of preterm birth.

KEY POINTS

- Prevalence of *Mycoplasma hominis* and *Ureaplasma urealyticum* during pregnancy depends on many factors: socioeconomic status, race, number of sexual partners, maternal and gestational ages, site of sampling and diagnostic method used, presence of other pathogens (such as BV) and adverse pregnancy outcomes.
- The gold standard for identification of *Mycoplasma hominis* and *Ureaplasma urealyticum* is culture. PCR is more sensitive, less time consuming and allows differentiation between genera and species.
- Growing evidences from clinical and experimental studies suggests that both cervicovaginal colonisation and/or amniotic fluid infection induce an inflammatory response resulting in chorioamnionitis, preterm labor, preterm premature rupture of membranes, all leading to potential adverse neonatal outcomes such as bronchopulmonary dysplasia.
- Clindamycin, erythromycin and azythromycin may prevent adverse pregnancy outcomes in patients colonized by *Mycoplasma hominis* and *Ureaplasma urealyticum*.
- Additional studies using different antibiotics are now warranted to elucidate the role of mycoplasma in each different adverse pregnancy outcome and to compare the different antibiotic regimen in terms of pharmacodynamics and efficacy.

CONFLICT OF INTEREST

The authors did not report any potential conflicts of interest.

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TABLES & FIGURE TITLES AND LEGENDS

All tables and figures presented in this paper are "originals". None were "previously published".

Figure 1:

1A:

For culture, samples should be inoculated in 10B broth under atmospheric conditions. Cultures are observed for up to 7 days for broth color change from yellow to pink, indicating pH change due to urease activity. Any broth with color change should be sub-cultured on A8 agar in 5% CO2 at 37°C. Colonies of *Ureaplasma* spp. (arrowhead) are identified by their characteristic brown appearance on A8 agar in the presence of the CaCl2 indicator. *M. hominis* (arrow) precipitate and show a typical ”fried-egg” aspect (low magnification).

1B:

Identification of *M. hominis* and *U. uraelyticum* using the Mycoplasma Duo kit (BioRAd, Nanterre, France). The kit must be read at 24 and 48 hours. Yellow and red media mean negative and positive cultures, respectively.

Wells 2 & 5 = negative controls

Wells 1 & 4 = *U. Urealyticum*

Wells 3 & 6 = *M. hominis*

Wells 4 & 6 = if positive, means $>10^4$ colonies / ml.

Table 1A & 1B:

1A: studies investigating the role of *U. Urealyticum* alone in adverse pregnancy outcomes.

1B: studies investigating the role of *M. hominis* alone or in combination with *U. Urealyticum* in adverse pregnancy outcomes.

PCR = Polymerase Chain Reaction or molecular methods, V = Vaginal swab, PPROM = Preterm Premature Rupture of Membranes, AF = amniotic fluid, PTL = Preterm Labor, P = Placenta, Chorio = chorioamnionitis

* Review of 12 published studies before 1989 [39].

** Review of 15 published studies before 1996 [14].

Table 2:

Antimicrobials susceptibilities to *U. urealyticm* and *M. hominis* isolates from samples obtained during pregnancy. Data were compiled from the following 5 studies:

Waites et al., Clin Micro Reviews, 2005 [4]

Bayraktar, Int J infect Dis, 2010 [10]

Choi, Ann Lab Med, 2012 [11]

De Francesco - J Infect Chemother – 2012 [33]

Gomez, J Matern Fetal Neonatal, 2007 [34]

MIC = Minimum Inhibitory Concentration

Table 3:

Studies investigating both molecular and cultures diagnostic methods for identification of *U. urealyticm* and *M. hominis* during pregnancy.

PCR = Polymerase Chain Reaction or molecular methods.

REFERENCE SECTION

•• Waites KB, J Mol Diag, 2012 [26]

This study critically reviews and summerizes the methods for detecting mycoplasmas and ureaplasmas in humans, and emphasizes molecular techniques.

•• Taylor-Robinson D, BJOG, 2011 [3]

This review studies the role of genital mycoplasmas in adverse outcomes of pregnancy, with particular focus in ther association with bacterial vaginosis.

•• Larsen B, Infect Dis Obst Gyn, 2010 [7]

This paper reviews the role of Mycoplasmas and Ureaplasmas in pathogenesis of adverse pregnancy outcome.

•• Waites KB, Clin Microb Rev, 2005 [4]

In this paper, the authors reviewed the pathogenesis of *Mycoplasmas* and *Ureaplasmas* genital tract infections in women and neonatal consequences.

•• Viscardi RM, Clin Perinatol, 2010 [12]

This study reviews the evidence supporting the role of *Ureaplasma* in the pathogenesis of preterm labor and lung and brain injury in neonates.

• Kacerovsky, AJOG, 2011 [20]

This study showed that histological chorioamnionitis is associated with a higher bacterial load of genital mycoplasmas in PPROM.

• Kacerovsky, AJOG, 2012 [21]

This very interesting paper demonstrates that intensity of intraamniotic inflammatory response to genital mycoplasmas decreased with gestational age.

• Choi SJ, Ann Lab Med 2012 [11]

This recent study investigates risk factors for vaginal infections and antimicrobial susceptibilities of *M. hominis* and *U. urealyticum* among women who experienced preterm birth.

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Table

Table 1A:

Published reports	Number of patients	Diagnostic method	Specimen	Condition studied	Controls	Study group	Statistical significance
Ureaplasma urealyticum							
Breugelmans M [19]	1988	Culture	V	PTL	41.4%	53.6%	<0.05
Harada K [50]	145	Culture	V	PTL	30%	51.1%	<0.05
Abele-Horn M [51]	295	Culture	V	PTL	51.8%	78.1%	<0.001
Abele-Horn M [52]	253	Culture	V	PTL	57.1%	89.7	<0.001
Carey JC [43]	4934	Culture	V	PTL	65.6%	66.5%	NS
Horowitz S [54]	362	Culture	V	PTL	42%	77%	<0.001
Kafetzis DA [22]	251	Culture	V	PTL	38%	36.5%	NS
Lamont RF [56]	88	Culture	V	PTL	46%	86%	<0.01
Donders GG [58]	228	Culture	V	PTL	4.1%	23.8%	<0.01
Kacerovský M [59]	450	Culture	V	PPROM	17%	68%	<0.001
Rezeberga D [60]	151	Culture	V	Chorio	26.6%	45.7%	NS
Horowitz S [54]	349	Culture	V	PPROM	42%	74%	<0.001
Horowitz S [55]	389	Culture	AF	PPROM	2.9%	17.8%	<0.01
Witt A [61]	207	Culture	AF + P	PPROM + PTL	2.7%	43.9%	<0.001
Horowitz S [62]	214	Culture	AF	PTL	2.8%	20%	<0.05
Choi SJ [11]	126	Culture	V	PTL	53.8%	60.9%	NS
Mitsunari M [63]	82	PCR	V	PTL	45.8%	87%	<0.001
Abele-Horn M [64]	198	PCR	V	Abortion	20%	42%	<0.05
Kataoka S [65]	877	PCR	V	PTL	8.8%	4.8%	NS
Govender S [66]	199	PCR	V	PTL	25%	25%	NS
Gerber S [67]	254	PCR	AF	PTL	5.3%	63%	<0.0001
Marconi C [18]	40	PCR	AF	PTL	0%	15%	NS
Namba F [25]	151	Culture	P	Chorio + PTL	-	42%	-
Yoon BH [68]	120	Culture	AF	PPROM	-	21%	-
Yoon BH [69]	181	Culture	AF	PTL	-	6.1%	-
Ogasawara KK [43]	51	Culture	V	PPROM + PTL	-	65%	-
Gauthier DW [70]	225	Culture	AF	PPROM	-	15%	-
Olomu IN [71]	866	Culture	P	PTL	-	6%	-
Kirchner L [72]	49	Culture	AF	PPROM + PTL	-	22%	-
Ogasawara KK [73]	60	Culture	V	PPROM + PTL	-	79.7%	-
Kundsin RB [74]	647	Culture	P	PPROM + PTL	-	28%	-
McDonald [75]	122	Culture	P	Abortions	-	17.2%	-
Yoon BH [76]	257	Culture/PCR	AF	PTL	-	7.1%	-
Yoon BH [77]	154	Culture/PCR	AF	PPROM	-	29.2%	-
Jacobsson B [78]	197	PCR	AF	PPROM	-	5.6%	-
Kacerovsky M [21]	145	PCR	AF	PPROM	-	24.1%	-
Kacerovsky M [20]	103	PCR	AF	PPROM	-	35.9%	-
Bujold E [79]	55	PCR	AF	Cervix insuff	-	9.1%	-
Grattard F [80]	208	PCR	V	PPROM + PTL	-	47.6%	-
Jacobsson B [81]	58	PCR	AF	PPROM	-	15.5%	-
Jacobsson B [82]	61	PCR	AF	PTL	-	3.3%	-
Lee S. I. [83]	977	Culture	V	PTL		3.7%	
Romero R* [13]	7133	Culture	V	Routine	70% (44-81%)	-	-
Carroll SG** [14]	24007	Culture	V	Routine	68% (35-90%)	-	-

Table 1B:

Published reports	Number of patients	Diagnostic method	Specimen	Condition studied	Controls	Study group	Statistical significance
Mycoplasma hominis							
Rezeberga D [60]	151	Culture	V	Chorio	4.8%	6.5%	NS
Kacerovský M [59]	450	Culture	V	PPROM	15%	28%	<0.001
Harada K [50]	145	Culture	V	PTL	6%	15.6%	<0.05
Donders GG [57]	228	Culture	V	PTL	1.5%	19%	<0.01
Lamont RF [56]	88	Culture	V	PTL	8%	24%	NS
Choi SJ [11]	126	Culture/PCR	V	PTL	3.8%	17.3%	NS
Kataoka S [65]	877	PCR	V	PTL	11%	19%	NS
Marconi C [18]	40	PCR	AF	PTL	5%	35.5%	<0.05
Nguyen DP [73]	456	PCR	AF	PTL	6.8%	33.3%	<0.05
Govender S [66]	199	PCR	V	PTL	63%	55%	NS
Nguyen DP [73]	456	PCR	AF	PTL	6.8%	33.3%	<0.05
Kundsin RB [74]	647	Culture	P	PPROM + PTL	-	6%	-
McDonald H. [75]	122	Culture	P	Abortions	-	2.5%	-
Kacerovsky M [21]	145	PCR	AF	PPROM	-	1.4%	-
Kacerovsky M [20]	103	PCR	AF	PPROM	-	2.9%	-
Grattard F [80]	208	PCR	V	PPROM + PTL	-	11%	-
Lee S. I. [83]	977	Culture	V	PTL		28.6%	
Romero R [13]	7133	Culture	V	PTL	27% (5-49%)	-	-
Carroll SG [14]	24007	Culture	V	Routine	27% (10-75%)	-	-
Ureaplasma urealyticum & Mycoplasma hominis							
Bayraktar MR [10]	100	Culture	V	PTL	4%	53%	<0.05
Goldenberg RL [23]	351	Culture	Cord blood	PTL	3.2%	34.7%	<0.001
Gonzalez Bosquet E [87]	250	Culture	V	PTL	32%	65%	<0.05
Donders GG [57]	759	Culture	V	PTL	1.2%	8.6%	<0.001
Penni SC	179	PCR	AF	PPROM	16.8%	100%	<0.001
Massaro G [88]	108	PCR	V	PPROM + PTL	23.3%	100%	<0.001
Caroll SG [14]	45	Culture	AF	PTL	-	27%	-
Berg TG [42]	2718	Culture	AF	PTL	1.8%	-	-

Table 2:

Antimicrobials	***Ureaplasma urealyticum*** MIC [µg/ml]	***Mycoplasma hominis*** MIC [µg/ml]
Erythromycin	0.2 - 2 - 4	> 128
Tetracyclin	0.05 - 2	0.02 - 2
Ciprofloxacin	0.1 - 16	0.1 - 4
Ofloxacin	0.2 - 25	0.1 - 64
Clarithromycin	≤ 0.004 - 2	16 - >256
Josamycin	0.5 - 4	0.05 - 2
Pristinamycin	0.1 - 1	0.1 - 0.5
Azithromycin	0.5 - 4	4 - 64
Doxycyclin	0.02 - 1	0.1 - 2

Table 3:

Published reports	Specimen	% positive by culture	% positive by PCR	% positive by culture and/or PCR
Ureaplasma urealyticum				
Choi SJ [11]	Vaginal	57.1%	16.7%	62.7%
Oh KJ [29]	Amniotic fluid	5.2%	19%	22.4%
Yoon BH [77]	Amniotic fluid	16%	28%	29.2%
Yoon BH [76]	Amniotic fluid	4.7%	5.9%	7.1%
Mycoplasma hominis				
Choi SJ [11]	Vaginal	4%	11.1%	12.7%

Figure 1A:

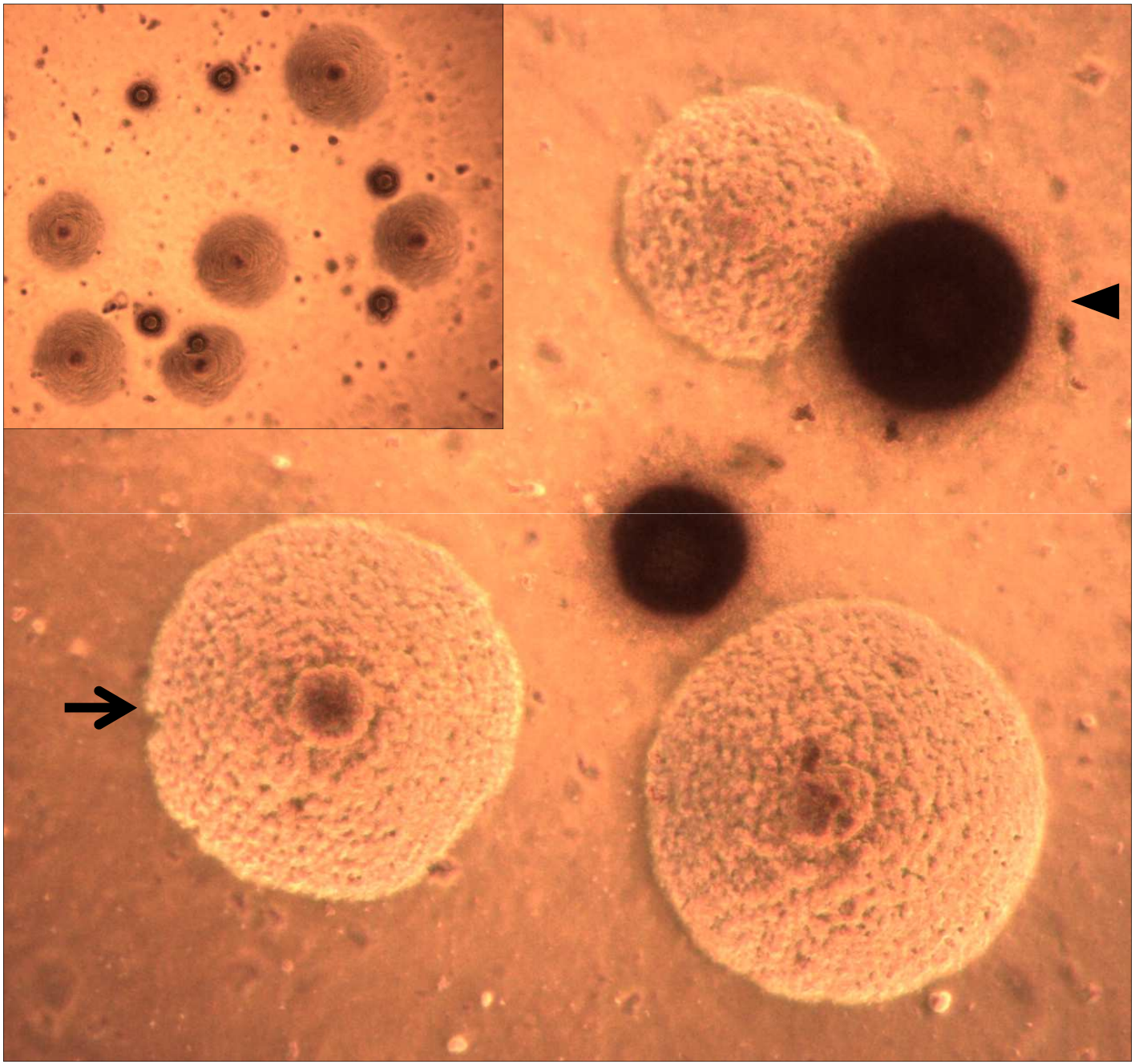
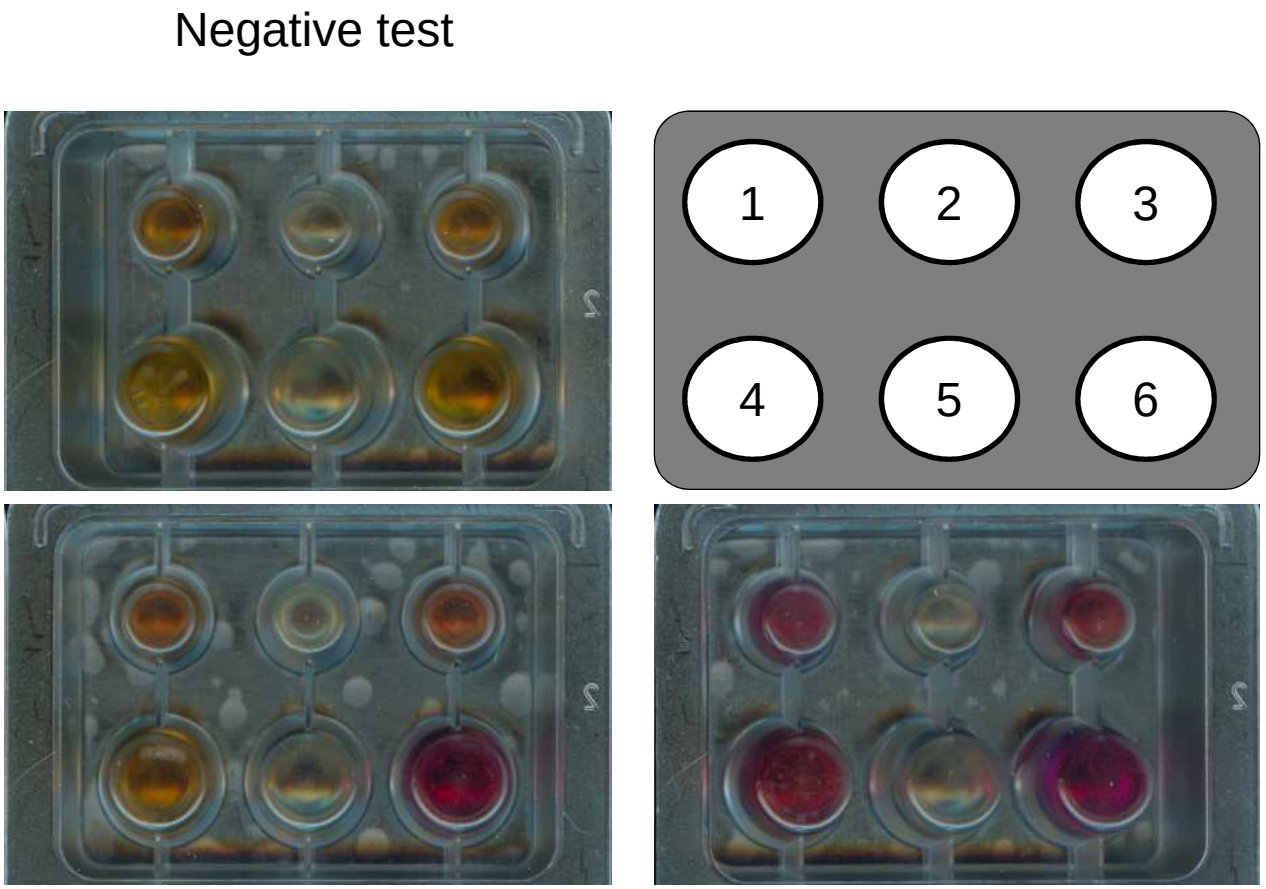


Figure 1B:


Negative test
1
2
3
4
5
6
Mycoplasma positive
Ureaplasma and
Mycoplasma positive