Seminars in Fetal & Neonatal Medicine 14 (2009) 190–199

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

# Congenital and opportunistic infections: *Ureaplasma* species and *Mycoplasma hominis*

Ken B. Waites [a,*], Robert L. Schelonka [b], Li Xiao [a], Peta L. Grigsby [c], Miles J. Novy [c]

[a] Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, USA
[b] Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, USA
[c] Division of Reproductive Sciences, Oregon National Primate Research Center, Beaverton, Oregon, USA

*Keywords:*
Bronchopulmonary dysplasia
Chorioamnionitis
Congenital infection
*Mycoplasma hominis*
Preterm labor
*Ureaplasma urealyticum*
*Ureaplasma parvum*

S U M M A R Y

There is strong evidence from clinical and experimental animal studies that ureaplasmas can invade the amnionic sac and induce an inflammatory response resulting in chorioamnionitis, preterm labor and neonatal lung injury. The ability of *Ureaplasma* spp. and *Mycoplasma hominis* to cause pneumonia, bacteremia, and meningitis in newborns can no longer be questioned. The association of *Ureaplasma* spp. with bronchopulmonary dysplasia has been supported by the majority of observational studies, but proof of causality is still lacking. The availability of molecular diagnostic technologies has enabled the designation of the two *Ureaplasma* biovars as individual species, but additional work must be done to establish whether there is differential pathogenicity between the *Ureaplasma* spp. or among their respective serovars. Future investigations to prevent prematurity should be directed toward identification and localization of specific micro-organisms combined with targeted antibiotic trials to determine whether such interventions can improve long-term infant outcomes.



## 1. Introduction

*Mycoplasma hominis* and *Ureaplasma* species have been associated with a variety of conditions that may affect the gravida, the developing fetus, and the neonate. For the gravida and fetus, these organisms may contribute to premature labor, chorioamnionitis, postpartum endometritis, growth restriction, spontaneous abortion and stillbirth; while the exposed neonate may develop pneumonia, bacteremia, meningitis, abscesses, and chronic lung disease. Despite numerous clinical, observational studies over a period of more than 30 years, the understanding of the clinical significance of these bacteria is far from complete. Several factors have led to confusion about these organisms and their disease associations: the high prevalence of the genital mycoplasmas in the lower urogenital tracts of healthy adults; their fastidious laboratory cultivation requirements; design limitations of many research studies; and reluctance of some clinicians to consider them as significant perinatal pathogens. Reviews on the cell biology, epidemiology, pathogenesis, clinical, diagnostic, and management aspects of genital mycoplasmas and their roles as neonatal pathogens have been published in recent years.[1–3] The present article describes the most current information on the role of genital mycoplasmas in premature birth and as neonatal pathogens, and offers insights for clinicians when to consider these organisms as agents of disease, and how to approach diagnosis and treatment.

## 2. Microbiological characteristics and epidemiology

### 2.1. Cellular biology and classification

Mycoplasmas and ureaplasmas are eubacteria that have evolved from clostridial-like Gram-positive cells by gene deletion. They are the smallest self-replicating organisms, both in genome size and cellular dimensions. They lack cell walls and exist in association with eukaryotic cells, mainly colonizing mucosal surfaces of the respiratory and urogenital tracts. Limited biosynthetic capabilities necessitate complex growth media containing sterols to provide components for the synthesis of their triple-layered cell membrane that provides structural support for these osmotically fragile microbes.

*Mycoplasma* and *Ureaplasma* species are included within the class Mollicutes, which is comprised of four orders, five families, eight genera, and nearly 200 known species, 17 of which are known to have humans as their primary host. Three species in the genus *Mycoplasma*, *M. hominis*, *M. genitalium* and *M. fermentans*, are known to occur in the female urogenital tract, have been associated with disease, and thus have potential implications for the fetus and

* Corresponding author. Departmentof Pathology, University of Alabama at Birmingham, WP 230, 619 19th Street South, Birmingham, AL 35249, USA. Tel.: +1 205 934 4960; fax: +1 205 975 4468.
*E-mail address:* waiteskb@uab.edu (K.B. Waites).

1744-165X/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.siny.2008.11.009

neonate. Members of the genus *Mycoplasma* do not have unique biochemical profiles sufficient to differentiate them from one another. However, ureaplasmas are unique among the mollicutes in that they hydrolyze urea to generate metabolic energy. The genus *Ureaplasma* contains 14 distinct serovars.[1] These serovars have been grouped by 16S rRNA sequencing into two genetically related clusters or biovars that are now designated as separate species. *U. parvum* contains serovars 1, 3, 6 and 14, whereas *U. urealyticum* includes the remaining ones (2, 4, 5, 7, 8, 9, 10, 11, 12 and 13).[4] There have been considerable efforts to determine whether one or the other of the two *Ureaplasma* spp. is more pathogenic in various clinical settings. More recently debate has extended to whether there is differential pathogenicity among the 14 serovars distributed between these two species. While some investigations have purported that there may be differences in pathogenic potential, this issue has not been settled and more work must be done before firm judgment can be rendered. A summary of evidence for and against differential pathogenicity of *U. parvum* and *U. urealyticum* is included in a recent review.[1]

### 2.2. Virulence factors and pathogenesis

Most mycoplasmal infections are limited to mucosal surfaces where they reside in close association and adherent to the host epithelium. The organisms rarely disseminate to other organ systems unless there is an underlying defect in host defense, as occurs in the developing fetus and preterm infant. Some species, such as *M. genitalium,* have specialized attachment tips that facilitate cytadherence. The cytadherence proteins of *M. hominis* and *Ureaplasma* spp. are not organized into a demonstrable attachment organelle and they have not been completely characterized. The *M. hominis* variable adherence-associated (Vaa) antigen is a size- and phase-variable adhesin which is highly immunogenic. The high variability of Vaa is presumably important for the diversity and host adaptation of this mycoplasma. Similar to the Vaa of *M. hominis*, the multiple-banded (MB) antigen of *Ureaplasma* spp. is immunogenic, undergoes a high rate of variation in vitro, may be involved in stimulation of the host inflammatory response, and is variable in size on invasive isolates. Each *Ureaplasma* serovar contains multiple MBA genes, and some serovars contain multiple copies of the same type of MBA gene. The variations in the MB antigens have been used as a basis to separate the two *Ureaplasma* species and to some extent to distinguish the serovars from one another. Ureaplasmas attach to host erythrocytes, neutrophils, spermatozoa, and urethral epithelial cells, and they can directly activate the first component of complement.[1] Both *M. hominis* and *Ureaplasma* spp. can induce inflammation in humans and this is a major factor involved in the production and manifestation of clinical disease.

Secretory products such as ammonia generated from metabolism of arginine by *M. hominis* and urea by *Ureaplasma* spp. may produce a local cytotoxic effect. Urease production by ureaplasmas has been implicated in urinary calculus production.[1] Even though phenotypic production of IgA protease and phospholipases by ureaplasmas was described several years ago, examination of the genomes of multiple serovars thus far has failed to reveal genes encoding these enzymes.[1,5] However, examination of the *U. parvum* genome has documented the presence of genes for two hemolysins.[5]

### 2.3. Urogenital colonization in adults

Most research in perinatal infections has focused on *M. hominis* and *Ureaplasma* spp. since they are the most common organisms isolated from the urogenital tracts of women and they are the most significant in terms of pathogenic potential in pregnant women and neonates. Following puberty, colonization of the male and female lower urogenital tracts by *M. hominis* and *Ureaplasma* spp. occurs as a result of sexual activity. Ureaplasmas can be isolated from cervicovaginal secretions from up to 80% of healthy women and >50% may harbor *M. hominis*. Their occurrence in pregnant women provides a reservoir for transmission to the fetus and neonate.

Other mycoplasmal species may be encountered in adults but they are uncommon in neonates. *M. pneumoniae* was not detectable by culture in 1500 neonates, but this mycoplasma has been transmitted transplacentally with subsequent detection from the nasopharynx from a neonate with congenital pneumonia.[6] *M. genitalium* has been demonstrated by the polymerase chain reaction (PCR) assay to occur in up to 20% of women with cervicitis or urethritis and may also cause pelvic inflammatory disease.[7] This mycoplasma may be found in a small percentage of pregnant women, but it has not been associated with bacterial vaginosis (BV), nor has its presence in the cervix been associated with adverse pregnancy or neonatal outcomes.[1] One case of vertical transmission from mother to neonate has been reported with *M. genitalium*.[8] *M. fermentans* was not detected by culture or PCR in women with cervicitis or urethritis, but it was detected in four of 232 amniotic fluids according to one study.[9] Histological evidence of chorioamnionitis and villitis in two of these women suggests it may cause inflammation, but there are no prospective studies demonstrating that this mycoplasma is associated with adverse pregnancy outcome or neonatal illnesses. A summary of perinatal conditions known to be caused by, or associated with, *M. hominis* and *Ureaplasma* spp. is provided in Table 1.

## 3. Genital mycoplasma infection as a cause of preterm birth

### 3.1. Routes of maternal infection and vertical transmission

Intrauterine infections may trigger premature labor and lead to preterm birth. The mechanisms by which intrauterine infections lead to preterm labor are related to activation of the innate immune system. Micro-organisms are recognized by pattern-recognition receptors (e.g. Toll-like receptors), which in turn elicit the release of inflammatory chemokines and cytokines. These cytokines, elaborated at the maternal–fetal interface, trigger prostaglandin production in the amnion, chorion, decidua and myometrium, leading to uterine contractions, cervical dilatation, membrane rupture and uterine contractions which further facilitate bacterial entry into the uterine cavity. Intra-amniotic infection (IAI) contributes to 40% of peripartum febrile illness and is associated with at least one-third of early-onset neonatal sepsis. The incidence increases with decreasing gestational age at delivery.[10] The prevalence of positive cultures and bacterial DNA in choriodecidual

**Table 1**
Maternal and neonatal conditions associated with or caused by genital mycoplasmas.

| Disease | *Ureaplasma* spp. | *M. hominis* |
|---|---|---|
| Bacterial vaginosis | ± | ± |
| Cervicitis | − | − |
| Pelvic inflammatory disease | − | + |
| Chorioamnionitis | + | − |
| Postpartum/postabortal fever | + | + |
| Spontaneous abortion | ± | ± |
| Preterm labor | + | − |
| Intrauterine growth retardation | ± | − |
| Congenital pneumonia | + | + |
| Neonatal chronic lung disease | ± | − |
| Neonatal bacteremia | + | + |
| Neonatal meningitis | + | + |
| Intraventricular hemorrhage | ± | − |
| Neonatal abscesses | + | + |

(−), no association or causal role demonstrated; (+), causal role; (±), significant association and/or strong suggestive evidence, but causal role not proven.