UREAPLASMA UREALYTICUM *AND* MYCOPLASMA HOMINIS *IN PRETERM LABOR*

UREAPLASMA UREALYTICUM E *MYCOPLASMA HOMINIS* NO PARTO PRÉ-TERMO

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ABSTRACT

Mycoplasma hominis and *Ureaplasma urealyticum* are considered genital mycoplasmas, because infection occurs through sexual contact. The presence of these bacteria has been associated with non gonococcal urethritis, cervicitis, vaginitis, pelvic inflammatory disease (PID) and pathology of pregnancy and newborns.Complications of genital mycoplasmas on the outcome of pregnancy include ectopic pregnancy, premature birth and preterm premature rupture of membranes (PPROM), chorioamnionitis, post partum endometritis, salpingitis, low weight and late abortion. This review article focuses on the importance of these microorganisms leading to preterm labor.

Keywords: *Mycoplasma hominis, Ureaplasma urealyticum*, preterm labor, STD

RESUMO

Mycoplasma hominis e *Ureaplasma urealyticum* são considerados micoplasmas genitais, pois a infecção ocorre através do contato sexual. A presença dessas bactérias tem sido associada A uretrite não gonocócica, cervicite, vaginite, doença inflamatória pélvica (DIP) e patologia da gravidez e de recém-nascidos. As complicações de micoplasmas genitais sobre os resultados da gravidez incluem gravidez ectópica, parto prematuro e ruptura prematura das membranas ovulares (PPROM), corioamnionite, endometrite pós-parto, salpingite, baixo peso e abortamento tardio. Este artigo de revisão concentra-se na importância destes microrganismos, levando a trabalho de parto prematuro.

Palavras-chave: *Mycoplasma hominis, Ureaplasma urealyticum,* trabalho de parto prematuro, DST

INTRODUCTION

Mycoplasmas are in the class *Mollicutes* (soft skin), the smallest free-living organisms, widespread in nature as parasites of mammals, reptiles, fish, arthropods and plants. Mycoplasmas are distinguished phenotypically from other bacteria by their minute size and total lack of a cell wall (they are bounded by a plasma membrane only), rendering them resistant to β-lactam-antibiotics[1,2].

Mycoplasmas constitute a large group of microorganisms, but only a few, i. e. *Mycoplasma* and *Ureaplasma species*, are pathogenic for humans, where they mainly inhabit the mucous membranes of the respiratory tract and genitourinary system. Three species have been isolated from the mucosal surfaces of the genitourinary tract: *Mycoplasma hominis* (*M. hominis*), *Ureaplasma urealyticum* (*U. urealyticum*) and the recently discovered *Mycoplasma genitalium* (*M. genitalium*)[3]. They are commonly referred to as "genital mycoplasmas", as the infection occurs via sexual contact. The role of mycoplasmas in the etiopathogenesis of inflammatory states of the genitourinary organ is still a subject of controversy[3]. Their presence has been associated with non-gonococcal urethritis, vaginitis, cervicitis, pelvic inflammatory disease (PID) and pathology of pregnancy and newborns[3]. *M. hominis* has been reported in 58-76% of women with bacterial vaginosis (BV) and is the only genital mycoplasma which is consistently more often isolated from vaginal swabs in women with BV than those without BV[4].

Ureaplasma species are the microorganisms most frequently isolated from amniotic fluid (AF) or placentae in women who deliver preterm between 23 and 32 weeks gestation[5-7]. Previously, there was only one known species of *Ureaplasma* found in humans (namely, *Ureaplasma urealyticum*) comprising 14 serotypes. In 2002, it was proposed to subdivide this species into *U. parvum*, comprising serotypes 1, 3, 6, and 14; and *U. urealyticum*, comprising serotypes 2, 4, 5, and 7 through 13[8,9]. Species differentiation might be important because previous studies[1,8] suggest that non-gonococcal urethritis and adverse pregnancy outcomes with respect to birth weight, gestational age, and preterm delivery are more implicated with the presence of *U. urealyticum* than with *U. parvum*[8].

Mycoplasmas may also be a component of the commensal flora of the genitourinary tract mucosa and may be found in the majority of sexually active humans[3]. The adverse effects of genital mycoplasmas on outcomes of pregnancy include ectopic pregnancy, preterm birth and PPROM, chorioamnionitis, postpartum endometritis, salpingitis, low birth weight and late miscarriage[10]. This review focuses on studies implicating mycoplasmas and preterm labor.

PATHOGENESIS OF MYCOPLASMAS

A. Adherence factors

The mycoplasmas are extracellular bacteria that adhere to epithelial cell surfaces. Thus, adherence proteins are one of their major virulence factors. Adhesion provides the opportunity for various metabolites of the mycoplasmas to induce cell injury or otherwise interfere with host metabolism[10].

B. Immunopathogenesis

Mycoplasmas can activate macrophages and monocytes, leading to the expression and secretion of the major proinflammatory cytokines: tumor necrosis factor (TNF)-α, IL (interleukin)-1β, IL-

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6, IL-8, IL-12, IL-16, interferon-γ[10]. Toll-like receptors (TLRs) on immune and epithelial cells recognize pathogen-associated molecular patterns (PAMPs), invariant structures on microorganisms, and activate an innate immune response. At present, 10 distinct members of the TLR family have been identified in man. TLR-2 is involved in the recognition of PAMPs on mycoplasmas[11].

EPIDEMIOLOGY

Colonization with *M. hominis* and *U urealyticum* can occur during birth but in most cases the infections are spontaneously cleared. Only in a small number of cases does colonization persist. However, when individuals become sexually active, colonization rates by mycoplasma increase. Approximately 15% of sexually active healthy women are colonized with *M hominis* and 45%-75% with *U. urealyticum*[7]. The carrier state is asymptomatic but the organisms can become opportunistic pathogens[2].

DETECTION TECHNIQUES

For *M. hominis* and the ureaplasmas, culture techniques were traditionally used for identification, but molecular-based techniques employing the sensitive polymerase chain reaction (PCR) increase the sensitivity of diagnosis. PCR techniques are now available for most mycoplasma and ureaplasma species of human origin and *M. genitalium*[1,12].

The elevated use of molecular techniques is likely to increase the detection of mycoplasmal infection among patients with obstetric complications. This was confirmed by a study in which amniocentesis was performed on 257 patients with preterm labor and intact membranes. *U. urealyticum* was detected in AF by PCR in 15 cases while only 9 cases were positive by culture. The clinical significance of being PCR positive and culture negative was evidenced by the observation that these women had a shorter median amniocentesis-to-delivery interval and higher AF interleukin-6 and white blood cell count than those who were negative by both PCR and culture. These women also had a higher rate of neonatal morbidity than those with a negative culture and PCR[1].

MYCOPLASMAS AND PRETERM LABOR

Preterm birth is a clinical syndrome characterized by uterine contractility, cervical ripening, and/or membrane rupture occurring before 37 weeks of gestation[13,14].

Preterm labor is a major challenge in obstetrics. Despite the advancing knowledge of risk factors and mechanisms related to preterm labor, the rate of preterm birth continues to increase in most industrialized countries[2]. In the U.S., the preterm delivery rate is 12-13%; in Europe and other developed countries, the reported rates are generally 5-9%[2]. Preterm birth accounts for 75% of perinatal mortality and more than half of the long term morbidity[2,13]. The mechanism of preterm labor is multifactorial and may be caused by infection, a vascular insult, uterine overdistension, an abnormal allogenic recognition, stress, or some other pathological process[15]. Preterm birth can be categorized by its clinical presentations: spontaneous preterm labor with intact membranes, preterm premature rupture of membranes (PPROM), and medically induced preterm birth for both maternal and fetal conditions (preeclampsia, abruption or placenta previa, intrauterine growth restriction, fetal distress, and uterine malformation)[2,7,16].

INTRAUTERINE INFECTION IN PRETERM

Intrauterine infection is a frequent and important mechanism leading to preterm birth. The mechanisms by which intrauterine infections lead to preterm labor are related to activation of the innate immune system. Microbial products bind to TLRs and activate proinflammatory cytokine production resulting in the subsequent stimulation of prostaglandins, other inflammatory mediators and matrix-degrading enzymes. Prostaglandins stimulate uterine contractility, whereas degradation of the extracellular matrix in the fetal membranes leads to PPROM[14,16]. Studies have demonstrated a link between preterm birth, bacterial infection in the upper genital tract, histologic chorioamnionitis and elevations in intraamniotic biochemical markers of an activated innate immune response[7,14,16]. There is evidence that intraamniotic infection may be a chronic process. Infection can be confined to the decidua, extend to the space between the amnion and chorion, or reach the amniotic cavity and the fetus[7,10].

Routes of intrauterine infection includes- (1) ascending from the vagina and the cervix,(2) hematogenous dissemination through the placenta, (3) accidental introduction at the time of an invasive procedure, (4) retrograde spread through the fallopian tubes. Many investigators believe that ascent of microorganisms from the lower to upper genital tract occurs during the second trimester, but the precise timing remains undetermined[2,7,14].

ROLE OF MYCOPLASMAS IN PRETERM LABOR

There have been numerous studies showing the potential importance of *M. hominis* and *Ureaplasma urealyticum* for inducing preterm labor. Inflammatory responses are more intense in intrauterine infections with genital mycoplasmas than with other microorganisms. In one study, AF was obtained by transabdominal amniocentesis or at the time of cesarean delivery in patients (n = 99) with PPROM and a positive AF culture. The white blood cell count in both AF and maternal blood, as well as plasma C--reactive protein concentrations were higher in patients with intraamniotic infection with mycoplasmas than in those with other micro-organisms[17].

Another study showed that when comparing mycoplasmal microorganisms to each other, *M. hominis* had a greater influence on production of an anti-inflammatory cytokine. This study looked at AF obtained by amniocentesis between 15-19 weeks of gestation in 179 asymptomatic women. The AF was tested for *M. hominis* and *U. urealyticum* by PCR, and for IL-1β, IL-1 receptor antagonist, IL-4, IL-6 and TNF-α. There was no relationship between *U. urealyticum* detection and the concentration of any cytokine. In contrast, detection of *M. hominis* was associated with elevated intra-amniotic concentrations of IL-4. This study also showed that all of the women with PPROM tested positive for either *U. urealyticum* or *M. hominis*[18].

Research performed on *rhesus monkeys* showed that mycoplasmas clearly induced preterm delivery and increased production of pro-inflammatory cytokines in these non-human primates. Seventeen *rhesus monkeys* received intraamniotic inoculations of clinical isolates of *Ureaplasma parvum* serovar 1, *M. hominis*, media control or physiological saline. Inoculations with either *U. parvum* or *M. hominis* resulted in early preterm delivery compared to control animals who had a spontaneous labor and delivery at term. In animals inoculated with *U. parvum* or *M. hominis*, there was a progressive increase in uterine activity from 48 to 72 hours after inoculation until preterm delivery. Inoculation with these mycoplasmas also led to significantly increased AF concentrations of TNF-α, IL-1β, IL-6 and IL-8 at 48 to 72 hours post-inoculation compared with pre-inoculation baseline values[5].

Asymptomatic intraamniotic infection with mycoplasmas may also increase the risk of preterm labor and delivery. AF was obtained by transabdominal amniocentesis from 254 asymptomatic women at 15-17 weeks gestation and tested for *U. urealyticum* by PCR. Preterm labor occurred in 58.6% of *U. urealyticum*-positive women compared with 4.4% of *U. urealyticum*-negative women. Preterm birth was documented in 24.1% of *U. urealyticum*-positive women as compared to only 0.4% of *U. urealyticum*-negative women. *U. urealyticum*-positive women also had a higher prevalence of preterm labor in a prior pregnancy (20.7%) than did the negative women[6].

A similar study looked at *M. hominis in* 456 women of european background. Transabdominal AF was obtained from these women at 15-17 weeks of pregnancy and tested by PCR. *M. hominis* was identified in 29 (6.4%) of the AF. The rate of preterm labor in women positive for *M. hominis* (14.3%) was higher than in the negative women (3.3%). Similarly, a spontaneous preterm birth with intact membranes occurred in 10.7% of the *M. hominis*-positive women as opposed to only 1.9% of the negative women[16].

An interesting cohort study provided evidence that the presence of bacteria in fetal membranes does not always result in preterm labor. It compared 50 infants who were delivered at ≤ 32 completed weeks of gestation with 52 infants who were delivered at term. Microorganisms were identified in the majority of the fetal membrane samples, including those from elective cesarean section at term (not in labor). Most preterm membranes contained bacteria; however membranes from preterm cesarean section from women not in labor were positive for bacteria as frequently as those collected from women with preterm labor or PPROM. This strongly suggests that the presence of bacteria is common in the pregnant uterus and insufficient by itself to cause preterm labor or PPROM[19]. These observations are consistent with a recent study demonstrating that during pregnancy mechanisms to increase tolerance to microbial invasion of the uterine cavity become more prominent[17].

TREATMENT

U. urealyticum and *M. hominis* are resistant to most of the common antibiotics that have been implicated for use against them[20,21]. Nevertheless, treatment with these antibiotics appears to decrease morbidity and the incidence of preterm birth. There is a case report of *U. urealyticum* isolation from the amniotic cavity of a woman with preterm labor at 27 weeks gestation who was treated with erythromycin base for 1 week, followed by fluoroquinolones and clindamycin for 10 days. A healthy neonate was delivered after spontaneous labor began at 33 weeks. The cultures obtained from the placenta and membranes were sterile[22].

A large retrospective analysis of 2,718 amniocentesis specimens revealed that, 44 patients were culture-positive for *Ureaplasma/Mycoplasma*. Thirty-five of these women were treated with oral erythromycin. Mid-trimester loss was 11.4% and 44.4% in the treated and untreated groups, respectively. Preterm delivery was similar in the two groups, which may indicate recolonization[23].

CONCLUSION

The evidence implicating genital mycoplasmas in initiating preterm labor and delivery is becoming more compelling. However, the presence of mycoplasmas in amniotic fluid from women who go on to deliver a normal neonate at term and the possibility that these microorganisms might be merely secondary consequences of infection by other bacteria still limits their acceptance as true pregnancy-associated pathogens. In our opinion, future research should focus on host factors that contribute to the transition of mycoplasmas from harmless commensal organisms to true pathogens in individual women.

Conflict of interests

The authors declare no conflict of interest.

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