Genital mycoplasmas infection in pregnancy

Abstract

Genital mycoplasmas are involved in many obstetrical complications. Preterm birth and preterm labor represent major factors that contribute to perinatal mortality and morbidity. Mycoplasma hominis has an important role in this problem, in association with bacterial vaginosis. Ureaplasmas, by citokine and inflammation production, must also be taken into account. Mycoplasma genitalium has a potential pathogenic role and should be treated in case of detection. There has been a lot of evidence regarding the role of M. hominis in postpartum and postabortum sepsis and on the role of ureaplasmas in chronic pulmonary disease and death of the very-low-birth-weight fetuses. The role of genital mycoplasmas in obstetrical complications is amplified by the presence or absence of bacterial vaginosis, an association that requires further research studies.

Keywords: *genital mycoplasmas, preterm birth, endometritis, chorioamniotitis, genital mycoplasmas treatment*

Rezumat

Micoplasmele genitale sunt implicate în numeroase complicații obstetricale. Nașterea prematură și travaliul prematur reprezintă factori importanți ce contribuie la mortalitatea și morbiditatea perinatală. Mycoplasma hominis joacă un rol important în această problemă, în asociere cu vaginoza bacteriană. Ureaplasmele, prin producția de citokine și inflamație, trebuie luate în calcul, de asemenea. Mycoplasma genitalium are un rol potențial patogenic și trebuie tratată, în caz de detecție. Au fost evidențiate numeroase dovezi în ceea ce privește rolul M. hominis în sepsisul post-partum și post-abortum și rolul ureaplasmelor în boala pulmonară cronică și în decesul nou-născuților cu greutate foarte mică la naștere. Rolul micoplasmelor genitale în complicațiile obstetricale este amplificat de prezența sau absența vaginozei bacteriene, asociere ce necesită studii de cercetare suplimentare.

Cuvinte-cheie: *micoplasme genitale, naștere prematură, endometrită, corioamniotită, tratamentul micoplasmelor genitale*

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Micoplasmele genitale în sarcină

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Introduction

The *Mollicute* class contains about 200 bacterial species, most of them belonging to the genus *Mycoplasma*. Of the 14 types of mycoplasmas found in humans, six of them mainly colonize the genitourinary tract, as in the case with the two species of human-specific *Ureaplasma*. *Mycoplasma hominis* and *Ureaplasma urealyticum* may be part of the commensal flora of women with active sexual life and may play an important role in the development of chorioamniotitis, salpingitis, bacterial vaginosis and postpartum endometritis. This article aims to provide an overview on the obstetrical complications that can be caused by mycoplasmas infection.

Epidemiology

The *in utero* infection with *Mycoplasma hominis* and/or *Ureaplasma* is more common after the rupture of membranes than in cases with intact membranes. The fetus colonization usually occurs due to the contact with the infected cervix or vagina during birth, therefore fetuses born by caesarean section are less frequently colonized[1,2]. The vertical mother-to-child transmission is very rare, with only one case reported, despite the fact that *Mycoplasma* was detected in the endometrium, cervix and vagina[3]. Neonatal colonization with *Mycoplasma hominis* and ureaplasmas disappears after the neonatal period, but there have been several cases in which they were detected in girls in the prepubertal period. After beginning the sexual activity, the risk of infection increases with the number of sexual partners. The prevalence of genital *Mycoplasma* infection is influenced by multiple factors. During pregnancy, hormonal and immunological changes may play a role. It is important to mention the strong influence of estrogen and progesterone on the colonization of the genital tract, demonstrated in mouse females, by different mycoplasmas[4].

Diagnostic methods

Regarding *Mycoplasma hominis* and ureaplasmas, culture techniques have been considered the gold standard for diagnosis, but this is a difficult method due to the fact that mycoplasmas require an environment with serum, metabolic substrate and growth factors. The absence of a rigid cell wall makes it almost impossible to visualize *Ureaplasma* under an optical microscope[5]. The molecular techniques such as polymerase chain reaction (PCR) may be essential for diagnosis, and there are currently available for most species of *Mycoplasma* and *Ureaplasma* of human origin. They are much more sensitive than cultures for diagnosis (requiring less than 100 copies of the genome), and the result is available in a single day[6]. PCR is an excellent alternative

to culture, but culture allows antibiotic susceptibility testing.

Mycoplasmas pathophysiology

The pathogenicity of mycoplasmas in the female genital tract has been confirmed by the presence of anti-*Mycoplasma* antibodies in women with intraamniotic infection and postpartum fever. Even before the appearance of antibodies, it has been shown that there is a recognition system that includes toll-like receptors that have been identified in the genital tract[7].

The adhesion of mycoplasmas to host cells is the starting point for pathogenicity, and membrane adhesion proteins of mycoplasmas play an important role on this line. The adhesion gives many *Mycoplasma* metabolites the opportunity to cause cell injury or to interfere with host metabolism. In addition, antigenic variation in modified proteins in the membrane of mycoplasmas allows the host's immune system to be bypassed. Numerous mycoplasmas also activate macrophages and monocytes, leading to the expression and secretion of proinflammatory cyrokines: TNF-α, interferon-γ, IL-1, IL-6, IL-12, IL-16, IL-1β, which have been associated with amniotic and placental infections. Interleukins 1β, 6 and 8, as well as TNF-α are typically elevated in amniotic fluid, umbilical cord blood and tissue containing bacterial DNA. Both inflammation and systemic and local infection are important in inducing pregnancy complications. The cascade mechanisms by which these complications occur involve bacterial endotoxins and membrane lipoproteins of the *Mycoplasma*, which activate the production of the aforementioned cytokines in the membranes and decidua. Endotoxins and cytokines stimulate the synthesis and release of prostaglandins, which lead to the production of proteases and other bioactive substances that can stimulate labor induction[8-12].

Mycoplasmas, *Ureaplasma* and pregnancy

Mycoplasma hominis is specifically associated with endometritis and preterm birth, while ureaplasmas are more frequently incriminated in chorioamniotitis, miscarriage, fetal death *in utero*, preterm birth, morbidity and perinatal mortality. Among mycoplasmas, ureaplasmas have a higher prevalence, *Ureaplasma parvum* being more frequently isolated than *Ureaplasma urealyticum*.

Ectopic pregnancy

The infection with the aforementioned pathogens may be associated with ectopic pregnancy. A history of pelvic inflammatory disease with involvement of the fallopian tubes increases the risk of ectopic pregnancy. Although it is well known that *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the main pathogens in the etiology of pelvic inflammatory disease, genital mycoplasmas may also be involved. There is no evidence to support the pathogenicity of ureaplasmas in pelvic inflammatory disease, but there is evidence to suggest the involvement of *Mycoplasma hominis* and *Mycoplasma genitalium* in the occurence of this pathology[13,14].

Bacterial vaginosis

Mycoplasma hominis may have a negative effect on pregnancy in association with bacterial vaginosis, some authors concluding that *M. Hominis* and *U. urealyticum* have been associated with an increased risk of miscarriage[16]. Regarding bacterial vaginosis, numerous studies have shown that women with bacterial vaginosis, symptomatic or not, have a much higher risk of late abortion and preterm birth. The treatment of bacterial vaginosis with metronidazole leads to the elimination of *M. hominis* infection, although it is resistant to metronidazole therapy, due to the fact that it is left without a favorable environment created by other bacteria in which to multiply. Therefore, it is difficult to know whether *M. hominis* is pathogenic in itself, or needs the presence of bacteria that cause bacterial vaginosis.

Regarding ureaplasmas, it is difficult to assess the negative impact on pregnancy in relation to bacterial vaginosis or its associated bacteria. While some studies have found no relationship between the presence of ureaplasmas and pregnancy loss, in others it has been shown that the isolation of these microorganisms was much more common in premature births, abortions and stillbirths than in the case of full-term births or after therapeutic abortion[1]. It is also important to mention the detection of ureaplasma in the placenta as an independent risk factor for chorioamniotitis in births below 32 weeks of gestation.

Preterm birth

Preterm birth due to preterm labor or premature rupture of membranes can be associated with genital mycoplasmas infection, by their ascent from the lower genital tract and penetration of the chorioamnius, with the invasion of the amniotic cavity and fetus infection[15]. Studies have shown the presence of bacteria in amniotic fluid in 13% of pregnant women with premature labor and intact membranes, while in pregnant women with premature ruptured membranes, the amniotic fluid cultures are positive at admission in 32% of patients and in 75% of them at the labor onset[17]. The examination of amniotic fluid has a high degree of predictability. Intraamniotic inflammation can be detected quickly by a metal-proteinase-8 matrix test, and the detection of ureaplasmas in amniotic fluid is more important than in the vagina or cervix.

Membrane inflammation is increased when it coexists with intraamniotic infection, and their association produces elevated levels of cytokines, important in producing the premature rupture of membranes. Intraamniotic inflammatory response is higher if there is an infection of the fluid than in the case of isolated chorionic infection. However, it is very difficult to determine whether fetal injury or death occurs due to the invasion of these mycoplasmas or whether their invasion occurs after fetal injury. In addition, the etiology is still questionable, as other microorganisms, especially those involved in bacterial vaginosis, are not considered. For example, in one study, the second-trimester placentas that contained numerous bacteria in the placental bed were analyzed, and they could not be identified by PCR[18].

Postpartum and postabortum fever

It is important to note that infections that lead to preterm birth and other complications of pregnancy do not end with birth. Fever is one of the effects after birth or abortion and can be explained by the passage of mycoplasmas into the blood. There have been reported cases in women with postpartum fever, from whom blood cultures were prelevated 1-2 days after birth, *M. hominis* being isolated. There is still no evidence to incriminate ureaplasmas on this line.

Complications for the newborn

The colonization of newborns with genital mycoplasmas can occur due to the rise of microorganisms in the lower genital tract of the pregnant woman during birth or by direct invasion of the fetus *in utero*. Genital mycoplasmas have produced congenital pneumonia, sepsis, meningitis and even death in fetuses with lower respiratory tract infections and low birth weight. In numerous studies, chronic premature lung disease or bronchopulmonary dysplasia has also been associated with the presence of ureaplasmas in the lower respiratory tract, probably due to persistent airway inflammation that produces a prolonged need for additional oxygen[19].

Genital mycoplasmas treatment during pregnancy

During pregnancy, the list of permitted and effective antibiotics against genital mycoplasmas is reduced. Macrolides and clindamycin are permitted. Erythromycin, the most widely used antibiotic in the treatment of pregnant women, has shown moderate efficacy over time. The only macrolide that has demonstrated increased efficacy against ureaplasmas and *M. hominis* is josamycin, which is allowed in pregnancy[6,20]. *M. genitalium* infections can be treated with azithromycin and josamycin, but resistance can be a problem.

The management of genital *Mycoplasma* infections depends very much on the understanding of their pathogenicity and the decision to treat empirically. The low presence of *Mycoplasma hominis* or ureaplasmas in the lower genital tract does not justify the treatment. However, in the case of *M. genitalium*, which has a higher pathogenicity, the treatment can be considered. Much more important, however, is the treatment at the beginning of pregnancy of symptomatic or asymptomatic bacterial vaginosis, in which *Mycoplasma hominis* is associated and to a lesser extent ureaplasmas, using broad-spectrum antibiotics, active also on *M. hominis* and ureaplasmas. The administration of ceftriaxone, clindamycin and erythromycin rarely removes the intraamniotic infection in women with premature rupture of membranes, either because the bacteria are resistant or partially protected from cell invasion or through the formation of biofilms. The clindamycin treatment in women with altered vaginal flora before 22 weeks demonstrated a significant decrease in the number of preterm births and low birth weight[21].

Postpartum or postabortum maternal fever due to *M. hominis* or ureaplasma usually remains untreated. If it is severe or persistent, the treatment should be guided by the results of blood cultures, not to mention the use of broad-spectrum antibiotics that are effective against bacteria responsible for bacterial vaginosis, such as clindamycin, which is also active on *M. hominis*, and clarithromycin, which has an increased efficacy against ureaplasmas.

For the newborns, if prophylactic antibiotic therapy has not been administered at the beginning of pregnancy, the treatment of respiratory disease or meningitis with the aforementioned antibiotics may be necessarry, depending on the result of the blood cultures. ■

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