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The impact of genital Ureaplasma infection versus Mycoplasma infection on preterm delivery

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ABSTRACT

Genital Mycoplasma spp. and Ureaplasma spp. infection is one of the most common infections in pregnancy. Most often the infection is latent and only late effects can be observed. During pregnancy, genital tract colonization with those germs is associated with poor obstetrical outcome, the most important being preterm premature rupture of membranes (PPROM) and preterm birth. Also, the neonatal morbidity is not neglectable. The particularity of the subject is that although the pregnancy's gold standard treatment is with Azithromycin, there were reported many cases of antibiotic resistance.

The main purpose of this article is to make a literature review in which to compare the impact of genital Mycoplasma spp. infection vs. Ureaplasma spp. infection on preterm delivery.The analysis was limited to articles written in English and published between March 2016 and August 2020 on PubMed, NCBI and medical journals.

This literature review shows the importance of gynecological screening, not only for Ureaplasma spp. and Mycoplasma spp., but for the entire abnormal vaginal flora as well, especially during pregnancy. Although both germs colonize the genital tract, Ureaplasma spp. has to be dreaded, its involvement in preterm delivery being a certainty.

Keywords: Mycoplasma, Ureaplasma, pregnancy, preterm birth

INTRODUCTION

Ureaplasma spp. (*U. parvum* and *U. urealyticum*) and *Mycoplasma hominis* are facultative anaerobic microorganisms which are usually found in the lower urogenital tract [1]. They belong to the Mycoplasmataceae family, which in terms of dimensions and genome span is known as the smallest form of life [2]. Those pathogens usually are transmitted sexually and can be detected in 40-80% of women, causing vaginitis, urinary tract infections, preterm delivery, chorioamnionitis, neonatal morbidity and postpartum endometritis [3].

Preterm birth has been defined by The World Health Organization (WHO) as any delivery before 37 completed weeks of gestation or less than 259 days since the first day of the woman's last menstrual period (LMP) [4].

The most common microorganisms found in the amniotic fluid of woman who presented spontaneous preterm labor despite they had intact membranes are Ureaplasma spp., *Mycoplasma hominis, Gardnerella vaginalis,* peptostreptococci and Bacteroides species. These are known as microorganisms with small pathogenicity but high involvement in preterm delivery and chorioamnionitis. Regarding preterm delivery the presumed mechanism is the ascent of the pathogens into the choriodecidual space and amniotic fluid, sometimes even in the first weeks of pregnancy. They can stay silent for months until the onset of the inflammatory processes, then will lead to cervical ripening, uterine contractions and, finally, preterm delivery [5].

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MATERIAL AND METHODS

PubMed, NCBI and medical journals were searched for studies written in English that analyzed the correlation between genital Mycoplasma and Ureaplasma infection on preterm birth. The studies have been published between March 2016 and August 2020.

The publications were selected taking in account the year of publication and the novelty they came with. The keywords used were: Mycoplasma, Ureaplasma, amniotic fluid, birth, delivery, preterm, inflammation, infection.

THE CONSEQUENCES OF THE COLONIZATION BY MYCOPLASMA/UREAPLASMA ON THE LOWER GENITAL TRACT

The pathogens causing intraamniotic inflammation, followed by intraamniotic infection are associated with a broad spectrum of conditions including women's infertility, recurrent spontaneous abortion, pelvic inflammatory disease, premature rupture of the membranes, preterm delivery, endometritis, chorioamnionitis and fetal infections [1].

From all the microorganisms mentioned above, we can't ignore the correlation between *Ureaplasma urealyticum* infection (alone or in association with *Mycoplasma hominis*) and some obstetrical complications. Over time, researchers found out that genital Mycoplasma infections involve a much more aggressive inflammatory response comparing with other pathogens [6].

Samples of *Mycoplasma hominis* were found in 30% of woman with intraamniotic infection. Furthermore, not only *Mycoplasma hominis*, but *Ureaplasma urealiticum* also, were found in vaginal samples, so the main conclusion is that coinfection is associated with worse prognosis. The incidence of preterm premature rupture of membranes and preterm birth is found higher in comparison with a single pathogen infection. According to studies, the colonization of pregnant women with those germs will drop gestational age at birth, birth weight and will rise the incidence of preterm delivery and chorioamnionitis [7].

THE RELATIONSHIP BETWEEN INTRAUTERINE GERMS COLONIZATION AND CHORIOAMNIONITIS

Chorioamnionitis includes many processes such as the inflammation of amnion, chorion and placenta. Usually, chorioamnionitis involves the amniotic fluid too. Chorioamnionitis can be classified as clinical and subclinical. Clinical forms of disease are manifested through fever, maternal tachycardia, fetal tachycardia, uterine tenderness and foul odor of amniotic fluid. On the other hand, the subclinical forms will remain silent and the diagnosis will be established microscopical after the membranes rupture and birth has already occurred.

Regarding Ureaplasma contamination, its presence during pregnancy is independently associated with chorioamnionitis, regardless of the trimester of pregnancy [8].

Histologically speaking, the infection reveals a chronic inflammation process characterized by mononuclear cells, macrophages and T lymphocytes located on the chorionic surface [9]. Although is still unclear if the microbial contamination precedes or determine choriodecidual inflammation, the intrauterine ascension of germs is considered the leading cause of PPROM and preterm delivery.

According to studies the main germs involved into the etiopathogenetic of chorioamnionitis are: *Ureaplasma urealiticum, Ureaplasma parvum, Mycoplasma hominis, Mycoplasma parvum, Staphylococcus aureus, Streptococcus mitis-Group, Escherichia coli, Enterococcus faecium, Staphilococcus hominis* and Klebsiella. Regarding the sequence chorioamnionitis – preterm delivery the researchers noticed that the most frequent germ involved is Ureaplasma spp. [2,5,10]. Also, they found a connection between genital Ureaplasma colonization, bacterial vaginosis, cervical-isthmic incompetence and obstetrical consequences and neonatal prognosis [10].

THE ROLE OF INFLAMMATION ON PRETERM DELIVERY – PATHOPHYSIOLOGIC CONSIDERATIONS

Looking over the results of both human and animal studies, the role of the intraamniotic infection on preterm labor and preterm delivery is not neglectable [11]. Regarding women with chorioamnionitis, labor and delivery are triggered by the activation and signaling of Toll-receptors. In this process are involved both the mother and the fetus. Toll-receptors are located on the surface of the amniotic epithelial cells, decidual cells, macrophages and neutrophils. As concerns the maternal component, the samples of chorion obtained from women who gave birth prematurely were compared immunohistological, the researchers concluded that the samples belonging to women with histological chorioamnionitis had a greater expression of Toll1 and Toll2 receptors. There are many factors involved in the up and down regulation of the placental Toll receptors, such as lipopolysaccharides and bacterial endotoxins, but also some microorganisms.

The *in vitro* experimental studies that have analyzed the inflammation cascade showed the following sequence: the activation of Toll receptors [2,4-6]

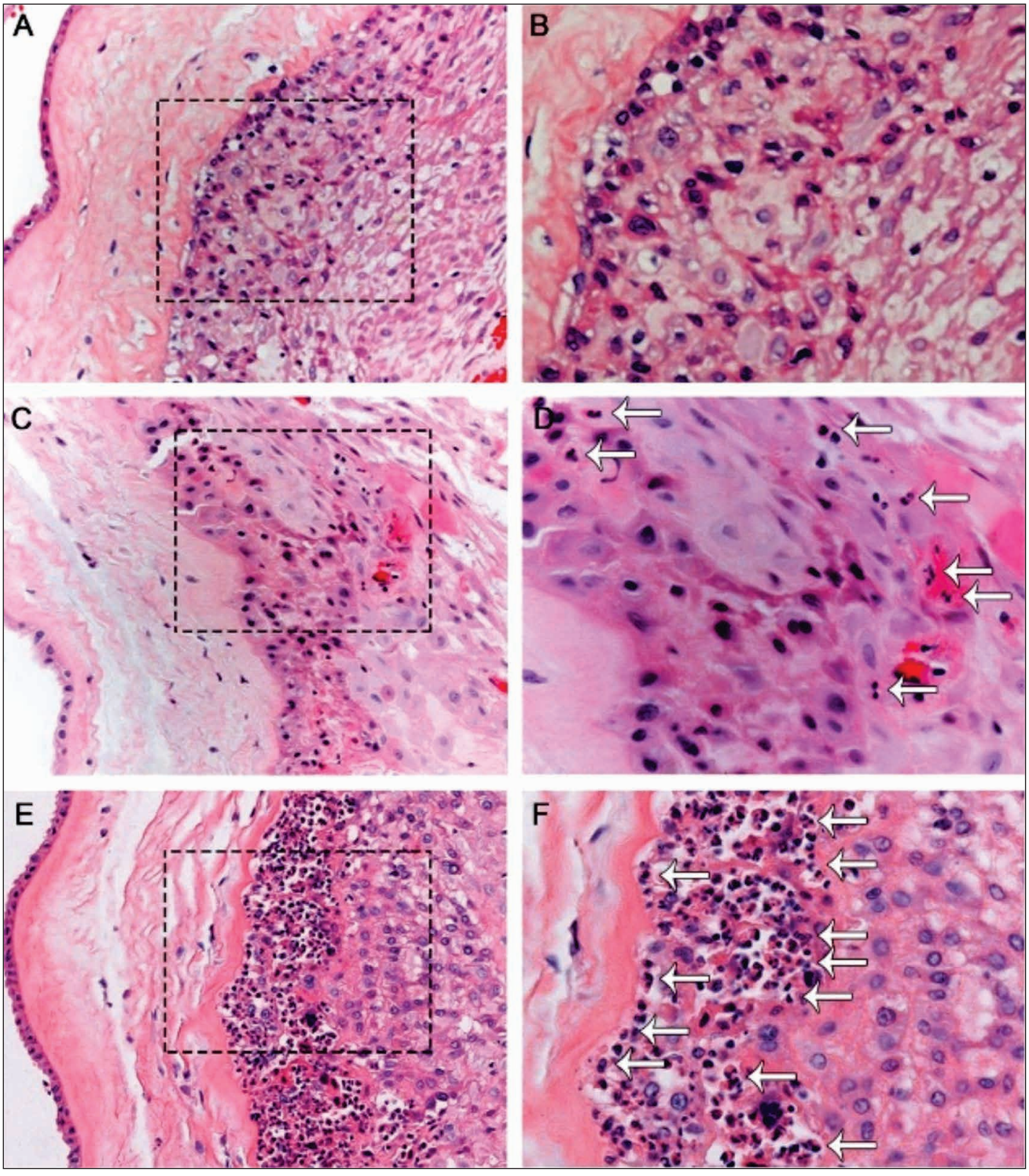

FIGURE 1. Comparation of histological aspect of the placenta in Ureaplasma infected women. The pictures above (A and B) show no signs of inflammation while the pictures below show mild/moderate inflammation (C and D) or severe (E and F). The arrow indicates neutrophils [9]

located on the amniotic cell surface triggers the nuclear kappa B factor signaling and also the release of proinflammatory cytokines MMP-9 and PGS2. In-vivo, inflammation mediators such as IL1β, IL6, IL8, TNF-α, G-CSF and chemotactic factors of monocytes were found in amniotic fluid, membranes and umbilical cord also. The main role of this cytokines and chemokines is the synthesis of prostaglandins, neutrophil infiltration, degranulation and the release of matrix metalloproteinases (MMPs). On a larger scale they determine cervix ripening, membranes weakening and eventually breaking. Linking the physiological inflammation mechanism from spontaneous parturition described above with the inflammation and the inflammatory mediators involved in the chorioamnionitis mechanism, it has

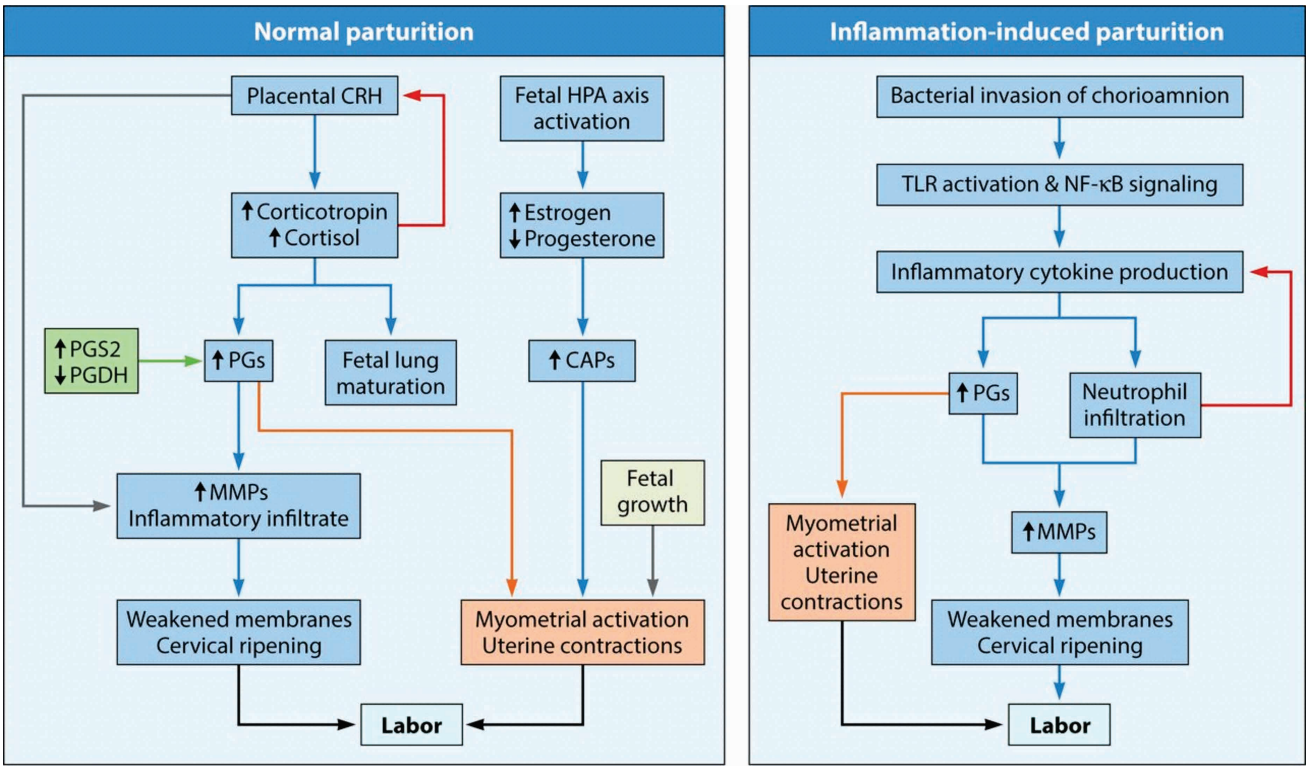

FIGURE 2. Schematic comparison between pathophysiology of normal induction of labor versus labor caused by chorioamnionitis [9]

been noticed that in membranes and amniotic fluid were found high levels of PG and MMPs in patients with chorioamnionitis also [9].

The increasing of MMP-8 concentration in the second trimester of pregnancy is highly linked with PPROM [12]. All the processes mentioned above couldn't be possible if the mucosal defense would be intact. *Ureaplasma urealiticum* and *Ureaplasma parvum* can synthesize IgA proteases, which will support the germ bypass the host loccal immune system, thereby they will settle on genital mucosa and then will ascend to the uterus and amniotic membranes [11]. It has been noticed that each Ureaplasma serotype has different level of infectivity. But when Ureaplasma spp. is coexisting with other germs, Ureaplasma promotes the Toll2 and Toll4 receptors signaling, also a faster activation of the inflammation mediators is produced such that Ureaplasma becomes both, pathogen and immunological factor [13].

A new theory regarding the involvement of neutrophils has been promoted lately. The neutrophils have a major role in extracellular matrix remodeling, particularly the collagen type IV from the amniotic membrane's matrix. The neutrophils influx occurred as a consequence of Ureaplasma infection, causes the collagen IV cleaving and the formation of phosphatidylglycerophosphate (PGP). PGP has a major role regarding polymorphonuclear chemotaxis, being involved in cysteine X cysteine (CXC) in the polymorphonuclear cell surface activation, reshaping the polymorphonuclear cell and is producing chemokines such as IL-8. In conclusion, Ureaplasma spp. infection promotes an inflammatory process in which will be released PGP and MMP-9. Those chemokines will attract neutrophils which will split collagen from the amniotic membrane's matrix, which will cause membrane rupture [12].

THE GENITAL TRACT COLONISATION WITH MYCOPLASMA AND/ OR UREAPLASMA DURING PREGNANCY – TO SCREEN OR NOT TO SCREEN

Genital Mycoplasma infection during pregnancy is a controversial subject which was discussed over for years. Mycoplasma and Ureaplasma pathogens colonize the genital tract of women and then remain silent for months, maybe years. The incidence is split into 80% for Ureaplasma and 10-20% for *Mycoplasma hominis* [14].

As concerns *Mycoplasma genitalium*, there is little information about it. Guides recommend screening for just a few categories of women such as symptomatic patients, asymptomatic patients who had intimate contact with positive partners and for those who will undergo an operation in the urogenital sphere. Regarding pregnancy, there are not yet known the *Mycoplasma genitalium* repercussions. What is known is the fact that studies do not recommend routine testing of pregnant women [15].

Regarding the diagnosis of intraamniotic Mycoplasma or/and Ureaplasma infection, the golden standard is amniocentesis follwed by polymerase chain reaction (PCR). Analyzing the outcome of studies, it was found that there were pregnant women with intact membranes and negative vaginal cultures but with positive amniotic fluid PCR who gave birth at term, which suggests that the main condition for PROM and preterm labor occurs is the presence of inflammation. Also, according to literature, there have been cited cases of intraamniotic infection with sterile cervical cultures.

The screening of Ureaplasma spp. / Mycoplasma spp. infection performed between 23 and 26 weeks of gestation has shown that there are several factors that can coexist and lead to poor obstetrical outcome such as maternal age, smoking and coinfection with other germs like *Trichomonas vaginalis*, bacterial vaginosis and, last but not least, the Mycoplasma and Ureaplasma spp. coinfection. So, the recommendation is to screen not only for Mycoplasma and Ureaplasma, but for the entire abnormal vaginal flora [14].

MANAGEMENT

Despite the evolution of medicine and the many therapeutic possibilites, the treatment of Mycoplasma and/or Ureaplasma infection during pregnancy is a continuous, challenge for the obstetricians. More than that, treatment became less effective if the PROM or preterm delivery occurred.

The golden standard treatment for urogenital Mycoplasms and/or Ureaplasms are tetracyclines and quinolones. Regarding the pregnancy, considering their adverse neonatal outcome those classes are forbidden, therefore the treatment of choice are macrolides, although empirical. The main inconvenience of this class is the microbial resistance, which is constantly rising [16].

Although with a great efficacy on vaginal and intraamniotic infection, there were described many cases of Azithromycin resistance. Regarding Erythromycin, several cases of therapeutic success have been reported. But, also, there are cases in which preterm birth occurred despite the various antibiotics association or how long they were administered. The literature described a case of a 27 weeks pregnant woman treated one week with Erythromycin, followed by ten days of Quinolones and Clindamycin, who gave birth at 33 weeks of gestation. On the microscopical examination of the membranes she had histological signs of ammonites. Clarithromycin has the property of penetrate the placental barrier, and in vitro performed studies proved the eradication of both germs. On the other side, neither antibiotics associations such as Ceftriaxone, Erythromycin and Clindamycin nor a longer administration, such as 10-40 days, haven't cured the intraamniotic infection. Also, they didn't reduce the inflammation or preterm delivery risk either. More than that, according to a double-blind randomized trial, Ureaplasma infection wasn't even remitted [14]. Until now, there were not reported cases of Doxycycline or Josamycin resistance, but as we mentioned above, there were reported cases of resistance for Azithromycin, Clarithromycin and Erythromycin [16].

To summarize, despite pharmacokinetics or the in-vitro studies results, neither Erythromycin, nor Azithromycin, administrated as mono or polytherapy or for a long period of time can reduce the PPROM or preterm birth. Clarithromycin seems to be the only promising option, but the researchers have not reported yet more data about its in-vivo efficacy [14].

CONCLUSIONS

This literature review shows the importance of gynecological screening, not only for Ureaplasma spp. and Mycoplasma spp., but for the entire abnormal vaginal flora. Screening is recommended for all pregnant women in the second and third trimester; nonpregnant women are also included. Despite the multiple diagnosis and treatment possibilities, the management of genital Mycoplasma and/or Ureaplasma infection during pregnancy remines a further challenge for obstetricians, especially due to antibiotic resistance. Further studies should be performed to identify the best treatment option.

Ureaplasma has a bigger prevalence regarding the genital colonization during pregnancy. Also, its' involvement in preterm delivery mechanism cannot be questioned. Fortunately, we can't say the same about Mycoplasma spp. The relationship between genital Mycoplasms and preterm birth is still unclear, Mycoplasms being less common and less studied. Data about their pregnancy's pathogenicity are missing as well. We cannot declare the Mycoplasm's involvement in the membrane rupture and preterm delivery; more studies should be pursued in this direction.

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