Antibiotic Treatment of Intra-Amniotic Infection with *Ureaplasma urealyticum*

A Case Report and Literature Review

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Abstract

Background: *Ureaplasma urealyticum* is the most common pathogen cultured from the amniotic cavity of women with preterm labor and intact membranes. However, experience with antibiotic eradication of the pathogen in this setting is limited. **Case:** We report a case of *U. urealyticum* isolation from the amniotic cavity of a woman with preterm labor at 27 weeks gestation. The patient 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, but the histopathology of the placenta revealed acute chorioamnionitis with acute funisitis. **Conclusion:** We suggest that intra-amniotic colonization with Mycoplasma spp. remote from term may be managed expectantly, and that therapy with fluoroquinolones and/or clindamycin may be an appropriate choice.

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Introduction

Microbial invasion of the amniotic cavity is found in 7–10% of patients with preterm labor and intact membranes [1, 2]. Moreover, the prevalence of a positive amniotic fluid culture increases with decreased cervical length as measured by transvaginal ultrasound, and reaches 26% for patients with a cervical length of <15 mm [1]. *Ureaplasma urealyticum* is the microorganism most frequently isolated from the amniotic fluid in these cases [1]. When compared to patients in preterm labor with a sterile amniotic fluid culture, patients with a positive culture for *U. urealyticum* tended to be at increased risk for clinical and histological chorioamnionitis, and for preterm delivery [3]. The neonates proved to be at increased risk for low Apgar scores, for neonatal sepsis, and for the development of bronchopulmonary dysplasia [3].

It has been suggested that eradicating *U. urealyticum* from the amniotic cavity may improve the obstetrical and neonatal outcomes of women in preterm labor [4]. However, to date no randomized controlled trial has addressed this issue. We present a case of preterm labor with proven *U. urealyticum* invasion of the amniotic cavity, where antibiotic therapy with erythromycin, fluoroquinolones and clindamycin was attempted with the result of pregnancy prolongation and a good neonatal outcome. We reviewed the extant literature for similar cases.

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Case Description

The patient was a 22-year-old primigravid healthy woman admitted at 27 gestational weeks for suspected preterm labor. She complained of mild lower abdominal pain (without fever, increased vaginal secretions or urinary symptoms) that had begun a day before admission. Prenatal care was normal and included triple test, extended anomaly scan, glucose tolerance test and routine serologies for rubella, cytomegalovirus, toxoplasma and syphilis. Upon admission, she was found to be in good general condition and her general physical examination was normal. The vital signs were: temperature 37°C, pulse 83, and blood pressure 131/69. The uterus was not tender, and its size was appropriate for gestational age. Occasional uterine contractions were palpated. On pelvic examination, the cervix was 80% effaced and dilated to 0.5 cm with vertex presentation at –3 station. The non-stress test (NST) was normal for gestational age with baseline heart rate of 140–150 beats/min. Irregular uterine contractions were also recorded. The ultrasound examination revealed a viable fetus, appropriate for gestational age, with a normal amniotic fluid index. A transvaginal ultrasound showed the cervical length to be 9 mm with funnel length of 10 mm. The initial laboratory results were: total white blood cell count 17,000/μl with 75.8% neutrophils, hemoglobin 10.4 g/dl, platelets 172,000/μl, and C-reactive-protein <3.0 mg/l. All other laboratory tests, including electrolytes, liver, renal and coagulation studies, were normal.

The patient was first treated with intravenous hydration, intra-muscular betamethasone 12 mg/day for 48 h, and oral tocolysis (nifedipine 20 mg every 4 h). We performed amniocentesis to rule out an intra-amniotic infection, and the findings were: normal amniotic fluid glucose of 34 mg/dl, and negative gram stain. The amniotic fluid was cultured on a blood agar media for bacteria with negative results after 72 h. Another culture for mycoplasma (on a media containing urea) yielded a *U. urealyticum* growth 7 days after the procedure. At that point, we repeated the amniocentesis in order to reconfirm the presence of intra-amniotic colonization. The second amniotic fluid sample was again positive for *U. urealyticum*. We discontinued the tocolytic treatment and initiated antibiotic treatment with oral ciprofloxacin 500 mg twice daily. This therapy was discontinued after 3 days because of an allergic pruritic reaction, and replaced with oral erythromycin base 500 mg three times daily for 7 additional days. After the completion of 10 days of antibiotic treatment, the patient (by now 30 weeks gestation) consented to a third amniocentesis, which was also positive for *U. urealyticum*. Again, amniotic fluid glucose, gram stain and standard bacterial culture were normal and negative, respectively. At that point, the antibiotic treatment was changed to intravenous clindamycin 600 mg three times daily plus oral levofloxacin 500 mg once daily for 10 additional days. All antibiotics were discontinued at 32 gestational weeks.

Throughout the whole period the patient was afebrile, with infrequent elevation to the subfebrile range (37.7–37.8°C). There were no uterine contractions either clinically or on NST, but progressive effacement and dilatation of the cervix took place. At 32 weeks gestation, a pelvic examination revealed 100% effacement, 2 cm dilation and bulging membranes. Other infectious sources were investigated: urine and blood cultures were negative, and chest X-ray was normal. Repeated NST were reactive, without fetal tachycardia or decelerations, and repeated modified biophysi-cal profiles were 10/10. Fetal interval growth scans were appropriate and consistent with dates.

Spontaneous labor started at 33 gestational weeks. The patient delivered a female newborn weighing 2,075 g, with Apgars 9, 10 (at 1 and 5 min, respectively). The maternal postpartum period was uneventful; the mother was afebrile and discharged after 3 days. The immediate neonatal course was complicated by a mild and transient respiratory distress. The subsequent neonatal course was normal, and the neonate was discharged aged 15 days, weighing 2,220 g. Cultures of the placenta were performed by using specimens obtained after separation of the chorioamniotic membranes. These specimens were cultured for standard bacteria and Mycoplasma, and both cultures were sterile. The histopathology of the placenta revealed acute chorioamnionitis with acute funisitis.

Discussion

U. urealyticum and *Mycoplasma hominis* are small, self-replicating prokaryotes that belong to the Mollicutes class. These organisms have been linked to adverse pregnancy outcomes such as preterm labor, preterm rupture of membranes, and preterm birth. Romero et al. [2] reported a positive amniotic fluid culture in 9.1% of 264 women in preterm labor with intact membranes; *U. urealyticum* was isolated in 6/24 (25%), and *M. hominis* in 4/24 (17%). Yoon et al. [3] reported a positive amniotic fluid culture in 9% of women in preterm labor. In almost 40% of the cases, the pathogen was *U. urealyticum*. Additionally, 2.5% of patients were found to have positive amniotic fluid PCR for *U. urealitycum* with negative culture.

In related studies, *U. urealyticum* colonization was discovered in routine genetic second trimester amniocentesis of asymptomatic women. Gray et al. [5] found only 8 women with positive cultures for *U. urealyticum* out of 2,461 women examined (0.24%); however, all 8 women had adverse obstetrical outcomes, such as spontaneous abortion (75%), preterm birth (25%), and neonatal death (12.5%). At pathology, all 8 placentas revealed chorioamnionitis, and 7 fetal lung tissues demonstrated pneumonia. Horowitz et al. [6] reported positive cultures in 2.8% of 214 patients. The pregnancies with positive cultures were complicated by spontaneous abortion (16.6 vs. 0.8% in the control group), or by other adverse obstetrical outcomes (50 vs. 12.2% in the control group). The rate of positive samples was higher when PCR was used to detect amniotic fluid *U. urealyticum*. Gerber et al. [7] reported a positive PCR in 11.4% of 254 women investigated. The incidence of preterm labor and preterm delivery was higher in PCR positive cases compared with con-

trols (58.6 vs. 4.4%, and 24.1 vs. 0.4%, respectively). Similarly, Nguyen et al. [8], testing the amniotic fluid from 456 samples of second trimester amniocentesis for *M. hominis* PCR, found that 6.4% of the samples were positive, and that the rate of preterm labor in women with positive PCR was higher than in the controls (14.3 vs. 3.3%).

In view of the studies that support the role of *U. urealyticum* in preterm labor, it is possible that antibiotic treatment may be beneficial in cases with proven amniotic cavity invasion by *U. urealyticum* [4]. Surprisingly, such a management has been reported in only three publications, two of which were case reports. Romero et al. [4] reported that *U. urealyticum* was eradicated from the amniotic fluid of a patient with premature rupture of membranes. Their patient was treated with erythromycin, ampicillin, gentamicin and clindamycin for 6 days. Mazor et al. [9] described a patient with preterm labor and a positive culture who was treated with erythromycin for 10 days. The repeat amniocentesis in this case was sterile. In the third report, by Berg et al. [10], 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, and their obstetrical outcomes were compared to 9 culture-positive untreated patients. The rates of second trimester spontaneous abortion were 11.4 and 44.4%, respectively, while the rates of preterm delivery were similar in the two groups (19.4 and 20%). In all three reports, erythromycin was used as the agent of choice for the eradication of *U. urealyticum*.

Mycoplasma spp. are susceptible to several classes of antimicrobial agents, of which the most commonly used are tetracyclines, macrolides, fluroquinolones and clindamycin. Macrolides and clindamycin are considered safe in pregnancy, while tetracyclines are contraindicated. However, macrolides may be inadequate for the treatment of intra-amniotic infection by Mycoplasma spp. In the first place, *U. urealyticum's* susceptibility to erythromycin is inferior to fluroquinolones [11]. Secondly, the transplacental transfer of macrolides is limited. Heikkinen et al. [12] reported that the in vitro mean transfer of erythromycin, roxithromycin and azithromycin across the human placenta were only 3.0, 4.3, and 2.6%, respectively. As for fluoroquinolones, although their use in pregnancy was associated with articular lesions in neonatal mice [13], this finding was not corroborated in the few studies on the use of fluoroquinolones in human pregnancy [14]. In the current case, we felt that treatment with fluoroquinolones was justified in view of the gestational age and the clinical severity.

Our patient presented with marked shortening of the cervical canal, without prior history or risk factors for cervical incompetence, and without significant uterine contractions. At presentation she was afebrile, and there where no systemic signs of infection except for leukocytosis. Amniotic fluid glucose and gram stain were normal. Unlike previous reports [9, 10], erythromycin treatment was ineffective in the eradication of *U. urealyticum* in our patient, as a culture from repeat amniocentesis following a 7-day regimen was positive. Possibly, this regimen was insufficient. Later, the patient was treated with a combination of clindamycin and levofloxacin. A repeat (fourth) amniocentesis was considered to be of limited clinical significance, and therefore was not performed. Consequently, we cannot definitely establish the efficacy of this combined treatment. We can presume that the negative postpartum cultures of the placenta indicate the eradication of *U. urealyticum* from the amniotic cavity.

Conclusion

In conclusion, an invasion of the amniotic cavity by *U. urealyticum* is associated with adverse pregnancy outcomes such as preterm labor. In two previous case reports, antibiotic treatment with erythromycin was advocated for *U. urealyticum* eradication. We report here for the first time that combined antibiotic treatment with fluoroquinolones (levofloxacin) and clindamycin is possibly more effective for *U. urealyticum* eradication. This therapy resulted in a significant prolongation of pregnancy (6 weeks) without any neonatal consequences. We suggest that rather than effecting immediate delivery, intra-amniotic colonization with Mycoplasma spp. remote from term may be managed expectantly. Clearly, this suggestion calls for randomized controlled trials.

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