

Eradication of Intra-Amniotic *Streptococcus mutans* in a Woman With a Short Cervix

Anne-Maude Morency, MD,¹ Fabien Rallu, PhD,¹ Céline Laferrière, MD, FRCPC,¹ Emmanuel Bujold, MD, FRCSC^{2,3}

¹Department of Microbiology, Centre Hospitalier Universitaire–Hôpital Sainte-Justine, Université de Montréal, Montreal QC

²Department of Obstetrics and Gynaecology, Centre Hospitalier Universitaire–Hôpital Sainte-Justine, Université de Montréal, Montreal QC

³Department of Obstetrics and Gynaecology, Faculté de médecine, Centre de recherche du CHUL, Centre Hospitalier Universitaire de Québec, Université Laval, Québec QC

Abstract

Background: Microbial invasion of the amniotic cavity (MIAC) remains an important pathogenetic factor in preterm births. Although most MIACs seem to originate in vaginal microflora, other reservoirs such as the oral microflora have been suggested.

Case: We report a case of successful eradication of *Streptococcus mutans* (a bacterium generally found in dental plaque) from the amniotic cavity, using ampicillin, gentamycin, and azythromycin in a woman who presented with threatened preterm labour and a short cervix at 25 weeks' gestation. She delivered at 34 weeks' gestation and was treated for tooth decay 12 weeks after delivery.

Conclusion: Intra-amniotic infection should be suspected in the presence of a short cervix during the second trimester. Appropriate parenteral antibiotics can eradicate intra-amniotic infection and potentially prolong pregnancy.

Résumé

Contexte : L'invasion microbienne de la cavité amniotique (IMCA) demeure un important facteur pathogène en ce qui concerne les naissances prématurés. Bien que la plupart des IMCA semblent trouver leur origine dans la microflore vaginale, on a laissé entendre qu'elles pouvaient provenir d'autres réservoirs, tels que la microflore orale.

Cas : Nous signalons un cas d'éradication réussie de *Streptococcus mutans* (une bactérie que l'on trouve habituellement dans la plaque dentaire) au sein de la cavité amniotique au moyen d'ampicilline, de gentamycine et d'azythromycine, chez une femme qui présentait une menace de travail préterme et un col court à la 25^e semaine de gestation. Elle a accouché à la 34^e semaine de gestation et a bénéficié d'un traitement contre la carie dentaire 12 semaines après l'accouchement.

Conclusion : Une infection intra-amniotique devrait être soupçonnée en présence d'un col court au cours du deuxième trimestre. L'administration parentérale d'antibiotiques appropriés peut éradiquer l'infection intra-amniotique et potentiellement prolonger la grossesse.

Key Words: Intra-amniotic infection, *Streptococcus mutans*, short cervix, preterm birth, pregnancy

Competing Interests: None declared.

Received on June 8, 2006

Accepted on August 2, 2006

J Obstet Gynaecol Can 2006;28(10):898–902

INTRODUCTION

Prematurity, the leading cause of neonatal morbidity and mortality, contributes to long-term neurocognitive deficits, pulmonary dysfunction, and ophthalmological disorders.¹ Microbial invasion of the amniotic cavity (MIAC) has emerged during the past few years as an important and frequent cause of premature labour, accounting for the majority of premature deliveries at less than 32 weeks of gestation.² In fact, the earlier the gestational age at delivery, the higher the frequency of MIAC in women with spontaneous preterm birth.³ Moreover, MIAC is associated with impending delivery and with fetal inflammatory response in women with preterm premature rupture of membranes or preterm labour.⁴

MIAC has been demonstrated in mid-trimester in asymptomatic women who subsequently delivered prematurely, suggesting a chronic pathogenetic process progressing over several weeks.^{5,6} Although randomized trials have shown that antibiotics do not delay delivery in symptomatic women with preterm labour, recent data indicate a potential benefit of antibiotics given earlier in pregnancy to asymptomatic women at high risk for preterm birth.^{7–9} Therefore, the early detection of MIAC allows treatment, with potential prevention of preterm delivery. In fact, mid-trimester short cervical length has recently been reported as the first manifestation of MIAC, with subsequent successful eradication of intra-amniotic *Ureaplasma urealyticum* and term delivery in several cases.⁸

The ascending route of microbial invasion from the vagina to the amniotic cavity has been considered the most probable pathway but does not seem to be the only one.^{10,11} A few years ago, Bearfield et al.¹² confirmed a link between

maternal oral flora and MIAC. They detected identical strains of *Streptococcus* species and *Fusobacterium nucleatum* in the amniotic fluid of pregnant women and on dental plaques. This finding is in agreement with other studies that showed an epidemiological association between gingivitis and preterm birth¹³⁻¹⁵ and with a recent randomized trial that demonstrated a decreased rate of low birth weight preterm births when mothers with gingivitis received periodontal therapy early in pregnancy.¹⁵

We report here a case of MIAC with *Streptococcus mutans*, a bacterium generally associated with dental plaque, in a woman who presented at 25 weeks' gestation with threatened preterm labour and a short cervix. Antimicrobial therapy resulted in subsequent negative amniotic fluid cultures and prolongation of the pregnancy.

THE CASE

A 33-year-old woman, gravida 2 para 1, with a prior full-term delivery, presented at 25 weeks and 4 days of gestation with irregular uterine contractions that had persisted for two days. She denied any other complaints, including bloody or clear vaginal fluid loss. Her medical, surgical, and dental histories were non-contributory. Her pregnancy had been uneventful to that point; an ultrasound examination at 19 weeks' gestation had shown fetal growth consistent with the gestational age. She was afebrile and had normal vital signs. On examination, there was no uterine tenderness or other clinical sign suggestive of chorioamnionitis. The cervix was closed, but 50% effaced. Transvaginal ultrasound showed a cervical length of 7 mm. Uterine monitoring demonstrated irregular contractions at 8- to 20-minute intervals with a reassuring fetal heart rate tracing.

The patient was transferred to a tertiary care centre because of the threatened preterm labour. A speculum examination performed on admission revealed visible fetal membranes (with transverse diameter < 1 cm). A second ultrasound examination revealed a cervical length of 4 mm, but no intra-amniotic sludge.^{16,17} The fetal heart rate tracing was reactive. A complete blood cell count (CBC) showed normal results. Urinalysis showed 20-30 erythrocytes and 5-10 leukocytes per microscopy field, but urine culture showed no growth. In view of the rapid cervical shortening, transabdominal amniocentesis was recommended to rule out intra-amniotic infection, but the patient did not consent to this procedure.⁸ She was subsequently treated empirically with azithromycin 500 mg daily by mouth for five days. Five days after the end of treatment, a third ultrasound examination revealed a cervical length of 0 mm. The patient then gave her consent for amniocentesis; when this was performed, intra-amniotic glucose was measured at 0.5 mmol/L, intra-amniotic lactate dehydrogenase (LDH) was 258 U/L,

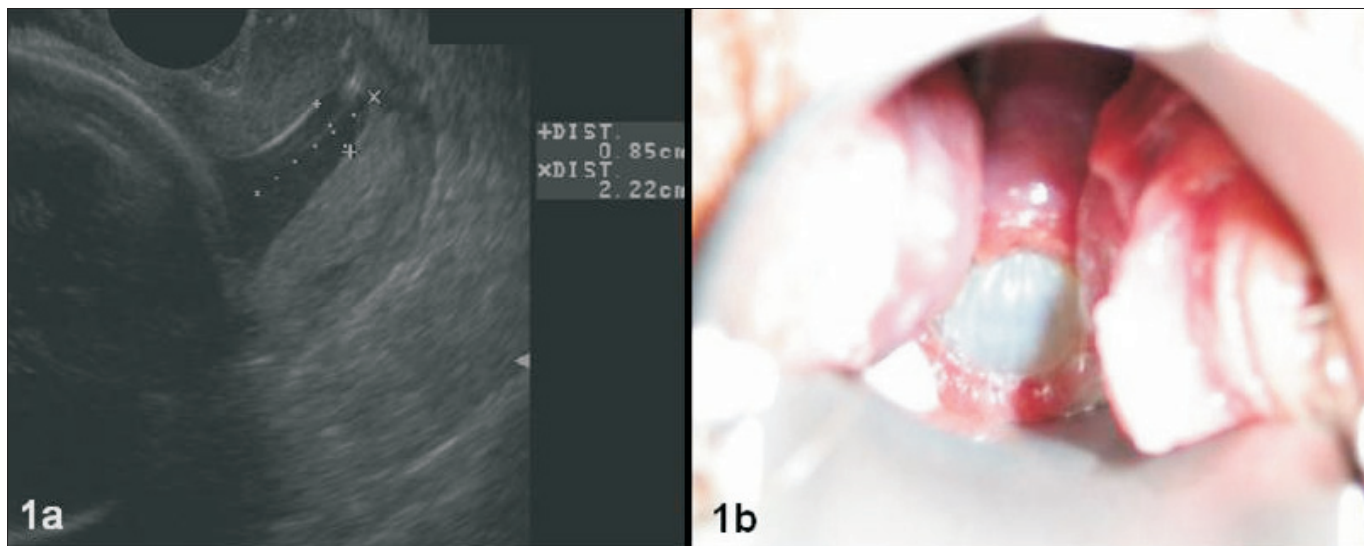
no polymorphonuclear (PMN) cells were seen on a smear, and direct Gram stain was negative.¹⁸⁻¹⁹ The amniotic fluid specimen was inoculated onto sheep blood, chocolate, MacConkey and anaerobic agar plates, cooked meat, and *Mycoplasma* and *Ureaplasma* broths. A further 3 mL and 7 mL of amniotic fluid were introduced into Bactec Peds plus and Bactec Lytic bottles respectively and incubated at 35°C in the Bactec System (BD-Canada, Oakville) generally used for blood cultures. Bacterial growth was detected in less than 24 hours in both bottles. Gram stain revealed positive cocci in pairs and chains. The patient then began treatment with a triple antimicrobial regimen that included ampicillin 2 g intravenously (IV) every six hours for 48 hours, followed by 1 g IV every six hours, gentamycin 120 mg IV initially followed by 80 mg IV every eight hours, and azithromycin 500 mg by mouth daily.

The patient was kept in hospital with activities limited to the use of bathroom, shower, and wheelchair. No tocolysis was used, and digital vaginal examinations were forbidden. Uterine contractions stopped spontaneously within the first 24 hours after the beginning of therapy. A *Streptococcus* bacterium (α -hemolytic and not *S. pneumoniae*) that was sensitive to penicillin, erythromycin, clindamycin, cefotaxime, and vancomycin was identified. The bacterium was further identified as *Streptococcus mutans* by 16S rDNA polymerase chain reaction (PCR) and sequencing techniques at the Quebec Public Health Laboratory. The antibiotic regimen was continued for a total of 10 days of ampicillin and five days of gentamycin and azithromycin. A fourth ultrasound examination and a second vaginal speculum examination done two days after the completion of antibiotic treatment showed no intra-amniotic sludge, a cervical length of 0 mm and visible fetal membranes with a diameter of 2-3 cm (Figure). A second amniocentesis was performed at 29 weeks and 4 days' gestation. Direct Gram stain of the amniotic fluid, fluid cultures and PCR as described above were negative. Amniotic fluid glucose was measured at 1.1 mmol/L, LDH at 287 U/L and no PMN cells were seen on smear.¹⁹

The patient was discharged home at 31 weeks' gestation. She was followed by weekly fetal non-stress tests. A third amniocentesis was performed at 34 weeks' gestation to confirm the eradication of *S. mutans*. Again, all cultures, PCR, and Gram stain of the fluid were negative. Fluid glucose was measured at 0.5 mmol/L, LDH at 314 U/L, and no PMN cells were seen on smear.

The patient presented to her health care centre two days after the amniocentesis with vaginal bleeding and a non-reassuring fetal heart rate tracing. An urgent Caesarean section was performed for suspected abruptio placentae. A normal infant girl weighing 2350 g was delivered, with Apgar scores of 3, 6, and 7 at one, five, and 10 minutes

Uterine cervix at 29 weeks' gestation. (a) Transvaginal ultrasound showing a very short cervical length and a large and long funnelling of membranes. (b) Speculum examination showing a dilated cervical os.



respectively. Arterial umbilical cord pH was measured at 7.13.

The postpartum period was uneventful, except for hyperbilirubinemia in the infant requiring phototherapy. Placental pathological examination revealed a circumvallate placenta with no evidence of vasculitis or inflammation. At twelve weeks postpartum, the patient's dentist found and treated a dental cavity. No cultures of the cavity were performed. Her sexual partner's dental examination revealed a large amount of dental plaque. Culture of an oral swab grew normal oral flora, but *S. mutans* was not found. The infant showed normal development at five months of age.

Interleukin 6 (IL-6) was subsequently measured in the residual amniotic fluid that had been stored at -80° Celsius. The levels of IL-6 were 2646, 3213, and 6060 ng/L in amniotic fluid from the first, second, and third amniocentesis, respectively, suggesting that the inflammatory process was never completely resolved.

DISCUSSION

We report the treatment and eradication of MIAC by *S. mutans*, using triple antibiotic therapy in a woman with threatened preterm labour and a short cervix. Other reports have described elimination of intra-amniotic infections with *U. urealyticum* and unidentified *Streptococcus viridans*.^{20–23} This is the first report of successful treatment of intra-amniotic *S. viridans* identified as *S. mutans*.

Measurement of cervical length is one of the most recently developed tools to predict preterm birth. Short cervical length, measured by transvaginal ultrasound and defined as

less than the tenth percentile for gestational age, or less than 25 mm, has been strongly associated with an increased risk of preterm birth, and normal cervical length has a high negative predictive value. However, treatment options are still unclear. Although cervical cerclage has been promising, the data are still contradictory about its benefits and indications.^{24–27} Sakai et al. recently showed that cerclage in the presence of increased levels of interleukin-8 in cervical mucus prior to the procedure was associated with a high rate of failure, whereas cerclage in the absence of inflammation was associated with a reduction in the risk of preterm birth.²⁸ This finding was in agreement with the findings of Mays et al., who showed that emergency cerclage was chiefly beneficial in women in whom intra-amniotic infection had been ruled out by amniocentesis prior to the surgical procedure.²⁹ Therefore, it seems that rescue cerclage for short cervix should be reserved for women in whom intracervical and intra-amniotic infection or inflammation have been ruled out. Moreover, the present case and others show that early detection and treatment of intra-amniotic infection can potentially prolong pregnancy.^{20–23} It is noteworthy that the intra-amniotic organisms grew in culture only when amniotic fluid was inoculated into blood-culture bottles (Bactec System), suggesting a low inoculum size. Increased sensitivity has already been demonstrated when body fluids such as synovial or peritoneal fluids are inoculated into blood-culture bottles.³⁰

The source of the intra-amniotic bacterium remains a question of interest in this case. Although 200 to 300 bacterial species have been associated with dental plaque, only the presence of *S. mutans* has been consistently linked to the

formation of human dental caries.³¹ Its presence in the vaginal flora is rare (0.2%), but it has been isolated in 4% of placental cultures.³² Although the origin of the bacterium in the present case has not been confirmed, it is possible that the dental decay found in the mother could have led to a transient bacteremia and resulted in MIAC. An infected oral cavity is a reservoir of bacteria and of inflammatory mediators such as prostaglandin E₂ and tumour necrosis factor- α ,^{12,33,34} both of which are associated with preterm labour. The bacteria could have also been introduced into the vagina during oral sex and into the amniotic cavity by the ascending route. This pathway has been proposed in a previously reported case of MIAC with *S. viridans*.³⁵ The presence of a large amount of dental plaque and a prior history of tooth decay in the patient's sexual partner supports this hypothesis.

CONCLUSION

Our experience with this patient shows that (1) intra-amniotic infection should be suspected when a short cervix is identified in mid-trimester, and (2) appropriate culture and treatment with parenteral antibiotics could potentially result in prolongation of a pregnancy affected by intra-amniotic infection.

ACKNOWLEDGMENTS

Dr Emmanuel Bujold holds a Clinician-Scientist Award funded by the Canadian Institutes of Health Research and the Jeanne and Jean-Louis Lévesque Research Chair for Perinatal Researches at the Faculté de Médecine, Université Laval, Québec, QC.

The editorial assistance of Ovid Da Silva is acknowledged.

The woman whose story is told in this case report has provided signed permission for its publication.

REFERENCES

- Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. *Semin Fetal Neonatal Med* 2004;9:429–35.
- Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med* 2000;342:1500–7.
- Watts DH, Krohn MA, Hillier SL. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. *Obstet Gynecol* 1992;79:351–7.
- Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. *Am J Obstet Gynecol* 1998;179:194–202.
- Gerber S, Vial Y, Hohlfeld P, Witkin SS. Detection of *Ureaplasma urealyticum* in second-trimester amniotic fluid by polymerase chain reaction correlates with subsequent preterm labor and delivery. *J Infect Dis* 2003;187:518–21.
- Cassell GH, Davis RO, Waites KB, Brown MB, Marriott PA, Stagno S, et al. Isolation of *Mycoplasma hominis* and *Ureaplasma urealyticum* from amniotic fluid at 16–20 weeks of gestation: potential effect on outcome of pregnancy. *Sex Transm Dis* 1983;10:294–302.
- King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database Syst Rev* 2002;4:CD000246.
- Hassan S, Romero R, Hendler I, Gomez R, Khalek N, Espinoza J, et al. A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. *J Perinat Med* 2006;34:13–9.
- Lamont RF, Sawant SR. Infection in the prediction and antibiotics in the prevention of spontaneous preterm labour and preterm birth. *Minerva Ginecol*. 2005;57:423–33.
- Benirschke K. Routes and types of infection in the fetus and the newborn. *Am J Dis Child* 1960;99:714–21.
- Romero R, Mazor M. Infection and preterm labor. *Clin Obstet Gynecol* 1988;31:553–84.
- Bearfield C, Davenport ES, Sivapathasundaram V. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. *BJOG* 2002;109:527–33.
- Lopez NJ, Smith PC, Gutierrez J. Higher risk of preterm birth and low birth weight in women with periodontal disease. *J Dent Res* 2002;81:58–63.
- Hasegawa K, Furuichi Y, Shimotsu A, Nakamura M, Yoshinaga M, Kamitomo M, et al. Associations between systemic status, periodontal status, serum cytokine levels, and delivery outcomes in pregnant women with a diagnosis of threatened premature labor. *J Periodontol* 2003;74:1764–70.
- Lopez NJ, Da Silva I, Ipinza J, Gutierrez J. Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. *J Periodontol* 2005;76:2144–53.
- Espinoza J, Gonçalves LF, Romero R, Nien JK, Stites S, Kim M, et al. The prevalence and clinical significance of amniotic fluid 'sludge' in patients with preterm labor and intact membranes. *Ultrasound Obstet Gynecol* 2005;25:346–52.
- Bujold E, Pasquier JC, Simoneau J, Arpin MH, Duperron L, Morency AM, et al. Intra-amniotic sludge, short cervix, and preterm delivery. *J Obstet Gynaecol Can* 2006;28:198–202.
- Bujold E, Chaiworapongsa T, Hammoud A, Berman S, Hendler I, Blackwell SC, et al. Lactate dehydrogenase in amniotic fluid: a rapid, sensitive, and widely available test for the detection of intra-amniotic inflammation. *J Obstet Gynaecol Can* 2004;26:S19.
- Romero R, Jimenez C, Lohda AK, Nores J, Hanaoka S, Avila C, et al. Amniotic fluid glucose concentration: a rapid and simple method for the detection of intraamniotic infection in preterm labor. *Am J Obstet Gynecol* 1990;163:968–74.
- Mazor M, Chaim W, Meirovitz M. Eradication of viridans streptococci from the amniotic cavity by parenteral antibiotic administration. A case report. *J Reprod Med* 1995;40:820–2.
- Mazor M, Chaim W, Hershkowitz R. Eradication of viridans streptococci from the amniotic cavity with transplacental antibiotic treatment. *Arch Gynecol Obstet* 1994;255:147–51.
- Romero R, Hagay Z, Nores J. Eradication of *Ureaplasma urealyticum* from the amniotic fluid with transplacental antibiotic treatment. *Am J Obstet Gynecol* 1992;166:618–20.
- Mazor M, Chaim W, Horowitz S. Successful treatment of preterm labour by eradication of *Ureaplasma urealyticum* with erythromycin. *Arch Gynecol Obstet* 1993;253:215–8.
- Althuisius SM, Dekker GA, Hummel P, Bekedam DJ, van Geijn HP. Final results of the Cervical Incompetence Prevention Randomized Cerclage Trial (CIPRACT): therapeutic cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2001;185:1106–12.
- Berghella V, Odibo AO, Tolosa JE. Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial. *Am J Obstet Gynecol* 2004;191:1311–7.

26. To MS, Alfirevic Z, Heath VC, Cicero S, Cacho AM, Williamson PR, et al. Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial. *Lancet* 2004;363:1849–53.
27. Romero R, Espinoza J, Erez O, Hassan S. The role of cervical cerclage in obstetric practice: can the patient who could benefit from this procedure be identified? *Am J Obstet Gynecol* 2006;194:1–9.
28. Sakai M, Shiozaki A, Tabata M, Sasaki Y, Yoneda S, Arai T, et al. Evaluation of effectiveness of prophylactic cerclage of a short cervix according to interleukin-8 in cervical mucus. *Am J Obstet Gynecol* 2006;194:14–9.
29. Mays JK, Figueroa R, Shah J, Khakoo H, Kaminsky S, Tejani N. Amniocentesis for selection before rescue cerclage. *Obstet Gynecol* 2000;95:652–5.
30. Bourbeau P, Riley J, Heiter BJ, Master R, Young C, Pierson C. Use of the BacT/Alert blood culture system for culture of sterile body fluids other than blood. *J Clin Microbiol* 1998;36:3273–7.
31. Loesche WJ. Role of streptococcus-mutans in human dental decay. *Microbiol Rev* 1986;50:353–80.
32. Rabe LK, Winterscheid KK, Hillier SL. Association of viridans group streptococci from pregnant women with bacterial vaginosis and upper genital tract infection. *J Clin Microbiol* 1988;26:1156–60.
33. Hill GB. Preterm birth: associations with genital and possibly oral microflora. *Ann Periodontol* 1998;3:222–32.
34. Han YW, Ikegami A, Bissada NF, Herbst M, Redline RW, Ashmead GG. Transmission of an uncultivated *Bergeyella* strain from the oral cavity to amniotic fluid in a case of preterm birth. *J Clin Microbiol* 2006;44:1475–83.
35. Gherman RB, Browning J, Tramont J, Eggleston MK. Streptococcus viridans intra-amniotic infection associated with antecedent cunnilingus. *Aust N Z J Obstet Gynaecol* 1999;39:257–9.