

Twenty percent of very preterm neonates (23-32 weeks of gestation) are born with bacteremia caused by genital *Mycoplasmas*

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Robert Goldenberg and the team at the University of Alabama report in this issue of the Journal that 23% of neonates who are born between 23 to 32 weeks of gestation have positive umbilical blood cultures for genital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*).¹ Newborns with positive blood cultures had a higher frequency of a neonatal systemic inflammatory response syndrome, higher serum concentrations of interleukin-6 and more frequent histologic evidence of placental inflammation (chorioamnionitis and funisitis) than those with negative cultures.¹

These observations are important because they underscore that (1) 1 of every 4 preterm neonates (23-32 weeks of gestation) is born with fetal bacteremia, (2) genital mycoplasmas are a frequent cause of congenital fetal infection, and (3) *U. urealyticum* was the most frequent isolate. Simultaneous colonization with *M. hominis* and *U. urealyticum* was present in 22% of newborns with a positive umbilical blood culture.

The article provides compelling evidence that congenital fetal infection is more frequent than was previously realized. The detection of genital mycoplasmas is not part of routine clinical practice in obstetrics and neonatology. Similarly, standard treatment for suspected neonatal sepsis does not include antibiotics that are effective against these microorganisms. Therefore, this report has important implications.

The data used in the article were derived from the Alabama Preterm Birth Study, which was sponsored by the National Institute of Child Health and Human Development/National

Institutes of Health. The study included 457 consecutive singleton pregnancies that delivered preterm between 23 and 32 weeks of gestation; 351 women/neonate pairs had umbilical cord blood cultures for genital mycoplasmas. Patients with spontaneous preterm delivery had a significantly higher rate of positive umbilical cord blood culture for *U. urealyticum* and/or *M. hominis* than those with indicated preterm delivery (34.7% vs 3.2%; $P < .0001$). The earlier the gestational age at delivery, the higher the rate of a positive umbilical cord blood culture. Neonates with a positive culture for *U. urealyticum* and/or *M. hominis* were more likely to have biochemical evidence of systemic inflammation, as determined by an elevated umbilical cord blood concentration of interleukin-6 (57.6% vs 19.7%; $P < .0001$), systemic inflammatory response syndrome (41.3% vs 25.7%; $P = .007$), and bronchopulmonary dysplasia (26.8% vs 10.1%; $P = .0001$). However, the association with bronchopulmonary dysplasia did not remain significant after adjusting for maternal race, gestational age at delivery, and neonatal gender.

The initial uncertainties about whether genital mycoplasmas can cause fetal/neonatal disease are disappearing in light of the accumulating evidence that these microorganisms have been implicated in neonatal sepsis,²⁻⁶ pneumonia,^{3,5-10} meningitis,^{4,11,12} and brain damage.¹³⁻¹⁶ Moreover, colonization of the neonatal respiratory tract with these organisms is a risk factor for chronic lung disease.^{3,17-21} A recent comprehensive review of the role of genital mycoplasmas by Waites et al²² updates the classic review of the subject by Cassell et al.²³

It is interesting to note that genital mycoplasmas are found frequently in the lower genital tract of sexually active women and normal pregnant women.²³⁻³⁰ Their presence alone constitutes neither evidence of disease nor a risk factor for preterm birth.³¹⁻³³ Yet, they are the microorganisms most frequently isolated from the amniotic fluid in women with preterm labor,³⁴⁻³⁸ preterm premature rupture of membranes,^{38,39} cervical insufficiency,⁴⁰ a short cervix,⁴¹ mid-trimester genetic amniocentesis,^{8,21,42-46} spontaneous labor at term,⁴⁷ term premature rupture of membranes,⁴⁸ and clinical chorioamnionitis.^{49,50} Therefore, a critical issue is why and how such microorganisms gain access to the amniotic cavity in some women but not in most. Whatever the explanation, it is now clear that these microorganisms can induce an inflammatory response in the amniotic cavity, fetus, and mother.⁵¹⁻⁵⁸

The findings of Goldenberg et al¹ raise important questions: (1) Should neonatal microbiologic work-up include the detection of genital mycoplasmas?; (2) If so, should this be undertaken with cultivation or molecular methods?; (3) Can screen-

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ing for neonatal bacteremia be accomplished in the clinical setting, rather than the research setting, with the use of umbilical cord blood?; (4) Should the antimicrobial treatment of suspected neonatal sepsis include antibiotics that are effective against *U. urealyticum* and/or *M. hominis*?; and (5) Can treatment of these organisms prevent the short- and long-term consequences of disease? Investigators have begun to address these questions.⁵⁹⁻⁶⁸

The seminal observations reported by Goldenberg et al stress the importance of the host-microbial interaction in the lower and upper genital tracts of pregnant women as well as in the fetus and neonate. ■

REFERENCES

1. Goldenberg RL, Andrews WW, Goepfert AR, et al. The Alabama Preterm Birth Study: Umbilical cord blood *Ureaplasma urealyticum* and *Mycoplasma hominis* cultures in very preterm newborns. Am J Obstet Gynecol 2008. [In press].
2. Kundsins RB, Driscoll SG, Monson RR, Yeh C, Bianco SA, Cochran WD. Association of *Ureaplasma urealyticum* in the placenta with perinatal morbidity and mortality. N Engl J Med 1984;310:941-5.
3. Cassell GH, Waites KB, Crouse DT, et al. Association of *Ureaplasma urealyticum* infection of the lower respiratory tract with chronic lung disease and death in very-low-birth-weight infants. Lancet 1988;2:240-5.
4. Waites KB, Rudd PT, Crouse DT, et al. Chronic *Ureaplasma urealyticum* and *Mycoplasma hominis* infections of central nervous system in preterm infants. Lancet 1988;1:17-21.
5. Waites KB, Crouse DT, Phillips JB III, Canupp KC, Cassell GH. Ureaplasma pneumonia and sepsis associated with persistent pulmonary hypertension of the newborn. Pediatrics 1989;83:79-85.
6. Brus F, van Waarde WM, Schoots C, Oetomo SB. Fatal ureaplasma pneumonia and sepsis in a newborn infant. Eur J Pediatr 1991;150:782-3.
7. Tafari N, Ross S, Naeye RL, Judge DM, Marboe C. Mycoplasma T strains and perinatal death. Lancet 1976;1:108-9.
8. Cassell GH, Davis RO, Waites KB, 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.
9. Quinn PA, Gillan JE, Markestad T, et al. Intrauterine infection with *Ureaplasma urealyticum* as a cause of fatal neonatal pneumonia. Pediatr Infect Dis J 1985;4:538-43.
10. Foulon W, Naessens A, Dewaele M, Lauwers S, Amy JJ. Chronic *Ureaplasma urealyticum* amnionitis associated with abruptio placentae. Obstet Gynecol 1986;68:280-2.
11. Garland SM, Murton LJ. Neonatal meningitis caused by *Ureaplasma urealyticum*. Pediatr Infect Dis J 1987;6:868-70.
12. Waites KB, Duffy LB, Crouse DT, et al. Mycoplasma infections of cerebrospinal fluid in newborn infants from a community hospital population. Pediatr Infect Dis J 1990;9:241-5.
13. Yoon BH, Romero R, Yang SH, et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. Am J Obstet Gynecol 1996;174:1433-40.
14. Yoon BH, Jun JK, Romero R, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. Am J Obstet Gynecol 1997;177:19-26.
15. Yoon BH, Romero R, Park JS, et al. Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 2000;182:675-81.
16. Dammann O, Allred EN, Genest DR, Kundsins RB, Leviton A. Antenatal mycoplasma infection, the fetal inflammatory response and cerebral white matter damage in very-low-birthweight infants. Paediatr Perinat Epidemiol 2003;17:49-57.
17. Sanchez PJ, Regan JA. *Ureaplasma urealyticum* colonization and chronic lung disease in low birth weight infants. Pediatr Infect Dis J 1988;7:542-6.
18. Wang EE, Frayha H, Watts J, et al. Role of *Ureaplasma urealyticum* and other pathogens in the development of chronic lung disease of prematurity. Pediatr Infect Dis J 1988;7:547-51.
19. Walsh WF, Stanley S, Lally KP, et al. *Ureaplasma urealyticum* demonstrated by open lung biopsy in newborns with chronic lung disease. Pediatr Infect Dis J 1991;10:823-7.
20. Payne NR, Steinberg SS, Ackerman P, et al. New prospective studies of the association of *Ureaplasma urealyticum* colonization and chronic lung disease. Clin Infect Dis 1993;17(suppl):S117-21.
21. Schelonka RL, Waites KB. *Ureaplasma* infection and neonatal lung disease. Semin Perinatol 2007;31:2-9.
22. Waites KB, Katz B, Schelonka RL. Mycoplasmas and ureaplasmas as neonatal pathogens. Clin Microbiol Rev 2005;18:757-89.
23. Cassell GH, Waites KB, Watson HL, Crouse DT, Harasawa R. *Ureaplasma urealyticum* intrauterine infection: role in prematurity and disease in newborns. Clin Microbiol Rev 1993;6:69-87.
24. McCormack WM. *Ureaplasma urealyticum*: ecologic niche and epidemiologic considerations. Pediatr Infect Dis 1986;5:S232-3.
25. McCormack WM, Rosner B, Alpert S, Evrard JR, Crockett VA, Zinner SH. Vaginal colonization with *Mycoplasma hominis* and *Ureaplasma urealyticum*. Sex Transm Dis 1986;13:67-70.
26. Iwasaka T, Wada T, Kidera Y, Sugimori H. Hormonal status and mycoplasma colonization in the female genital tract. Obstet Gynecol 1986;68:263-6.
27. Luton D, Ville Y, Luton-Sigy A, et al. Prevalence and influence of *Mycoplasma hominis* and *Ureaplasma urealyticum* in 218 African pregnant women and their infants. Eur J Obstet Gynecol Reprod Biol 1994;56:95-101.
28. Paul VK, Gupta U, Singh M, Nag VL, Takkar D, Bhan MK. Association of genital mycoplasma colonization with low birth weight. Int J Gynaecol Obstet 1998;63:109-14.
29. Aaltone R, Jalava J, Laurikainen E, Karkkainen U, Alanen A. Cervical *Ureaplasma urealyticum* colonization: comparison of PCR and culture for its detection and association with preterm birth. Scand J Infect Dis 2002;34:35-40.
30. Barton PT, Gerber S, Skupski DW, Witkin SS. Interleukin-1 receptor antagonist gene polymorphism, vaginal interleukin-1 receptor antagonist concentrations, and vaginal *Ureaplasma urealyticum* colonization in pregnant women. Infect Immun 2003;71:271-4.
31. Romero R, Mazor M, Oyarzun E, Sirtori M, Wu YK, Hobbins JC. Is genital colonization with *Mycoplasma hominis* or *Ureaplasma urealyticum* associated with prematurity/low birth weight? Obstet Gynecol 1989;73:532-6.
32. Eschenbach DA, Nugent RP, Rao AV, et al. A randomized placebo-controlled trial of erythromycin for the treatment of *Ureaplasma urealyticum* to prevent premature delivery: the Vaginal Infections and Prematurity Study group. Am J Obstet Gynecol 1991;164:734-42.
33. Carey JC, Blackwelder WC, Nugent RP, et al. Antepartum cultures for *Ureaplasma urealyticum* are not useful in predicting pregnancy outcome: the Vaginal Infections and Prematurity Study group. Am J Obstet Gynecol 1991;164:728-33.
34. Romero R, Mazor M. Infection and preterm labor. Clin Obstet Gynecol 1988;31:553-84.
35. Watts DH, Krohn MA, Hillier SL, Eschenbach DA. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. Obstet Gynecol 1992;79:351-7.
36. Kundsins RB, Leviton A, Allred EN, Poulin SA. *Ureaplasma urealyticum* infection of the placenta in pregnancies that ended prematurely. Obstet Gynecol 1996;87:122-7.
37. Yoon BH, Romero R, Lim JH, et al. The clinical significance of detecting *Ureaplasma urealyticum* by the polymerase chain reaction in the am-

- niotic fluid of patients with preterm labor. *Am J Obstet Gynecol* 2003;189:919-24.
38. Witt A, Berger A, Gruber CJ, et al. Increased intrauterine frequency of *Ureaplasma urealyticum* in women with preterm labor and preterm premature rupture of the membranes and subsequent cesarean delivery. *Am J Obstet Gynecol* 2005;193:1663-9.
39. Gomez R, Romero R, Nien JK, et al. Antibiotic administration to patients with preterm premature rupture of membranes does not eradicate intra-amniotic infection. *J Matern Fetal Neonatal Med* 2007;20:167-73.
40. Romero R, Gonzalez R, Sepulveda W, et al. Infection and labor. VIII. Microbial invasion of the amniotic cavity in patients with suspected cervical incompetence: prevalence and clinical significance. *Am J Obstet Gynecol* 1992;167:1086-91.
41. Hassan S, Romero R, Hendler I, et al. A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. *J Perinat Med* 2006;34:13-9.
42. Gray DJ, Robinson HB, Malone J, Thomson RB Jr. Adverse outcome in pregnancy following amniotic fluid isolation of *Ureaplasma urealyticum*. *Prenat Diagn* 1992;12:111-7.
43. Horowitz S, Mazor M, Romero R, Horowitz J, Glezerman M. Infection of the amniotic cavity with *Ureaplasma urealyticum* in the mid trimester of pregnancy. *J Reprod Med* 1995;40:375-9.
44. 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.
45. Nguyen DP, Gerber S, Hohlfeld P, Sandrine G, Witkin SS. *Mycoplasma hominis* in mid-trimester amniotic fluid: relation to pregnancy outcome. *J Perinat Med* 2004;32:323-6.
46. Perni SC, Vardhana S, Korneeva I, et al. *Mycoplasma hominis* and *Ureaplasma urealyticum* in mid trimester amniotic fluid: association with amniotic fluid cytokine levels and pregnancy outcome. *Am J Obstet Gynecol* 2004;191:1382-6.
47. Romero R, Nores J, Mazor M, et al. Microbial invasion of the amniotic cavity during term labor: prevalence and clinical significance. *J Reprod Med* 1993;38:543-8.
48. Romero R, Mazor M, Morrotti R, et al. Infection and labor: VII, microbial invasion of the amniotic cavity in spontaneous rupture of membranes at term. *Am J Obstet Gynecol* 1992;166:129-33.
49. Blanco JD, Gibbs RS, Malherbe H, Strickland-Cholmley M, St Clair PJ, Castaneda YS. A controlled study of genital mycoplasmas in amniotic fluid from patients with intra-amniotic infection. *J Infect Dis* 1983;147:650-3.
50. Cassell GH, Waites KB, Gibbs RS, Davis JK. Role of *Ureaplasma urealyticum* in amnionitis. *Pediatr Infect Dis* 1986;5:S247-52.
51. Gibbs RS, O'Dell TN, MacGregor RR, Schwarz RH, Morton H. Puerperal endometritis: a prospective microbiologic study. *Am J Obstet Gynecol* 1975;121:919-25.
52. Phillips LE, Faro S, Pokorny SF, Whiteman PA, Goodrich KH, Turner RM. Postcesarean wound infection by *Mycoplasma hominis* in a patient with persistent postpartum fever. *Diagn Microbiol Infect Dis* 1987;7:193-7.
53. Maccato M, Faro S, Summers KL. Wound infections after cesarean section with *Mycoplasma hominis* and *Ureaplasma urealyticum*: a report of three cases. *Diagn Microbiol Infect Dis* 1990;13:363-5.
54. Newton ER, Prihoda TJ, Gibbs RS. A clinical and microbiologic analysis of risk factors for puerperal endometritis. *Obstet Gynecol* 1990;75:402-6.
55. Roberts S, Maccato M, Faro S, Pinell P. The microbiology of post-cesarean wound morbidity. *Obstet Gynecol* 1993;81:383-6.
56. Yoon BH, Chang JW, Romero R. Isolation of *Ureaplasma urealyticum* from the amniotic cavity and adverse outcome in preterm labor. *Obstet Gynecol* 1998;92:77-82.
57. Yoon BH, Romero R, Park JS, et al. Microbial invasion of the amniotic cavity with *Ureaplasma urealyticum* is associated with a robust host response in fetal, amniotic, and maternal compartments. *Am J Obstet Gynecol* 1998;179:1254-60.
58. Yoon BH, Romero R, Kim M, et al. Clinical implications of detection of *Ureaplasma urealyticum* in the amniotic cavity with the polymerase chain reaction. *Am J Obstet Gynecol* 2000;183:1130-7.
59. Izraeli S, Samra Z, Sirota L, Merlob P, Davidson S. Genital mycoplasmas in preterm infants: prevalence and clinical significance. *Eur J Pediatr* 1991;150:804-7.
60. Abele-Horn M, Hentschel J. [*Ureaplasma urealyticum* in newborn and premature infants; its association with bronchopulmonary dysplasia]. *Dtsch Med Wochenschr* 1992;117:408-14.
61. Heggie AD, Jacobs MR, Butler VT, Baley JE, Boxerbaum B. Frequency and significance of isolation of *Ureaplasma urealyticum* and *Mycoplasma hominis* from cerebrospinal fluid and tracheal aspirate specimens from low birth weight infants. *J Pediatr* 1994;124:956-61.
62. Waites KB, Sims PJ, Crouse DT, et al. Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for *Ureaplasma urealyticum* infection. *Pediatr Infect Dis J* 1994;13:287-93.
63. Pacifico L, Panero A, Roggini M, Rossi N, Bucci G, Chiesa C. *Ureaplasma urealyticum* and pulmonary outcome in a neonatal intensive care population. *Pediatr Infect Dis J* 1997;16:579-86.
64. Bowman ED, Dharmalingam A, Fan WQ, Brown F, Garland SM. Impact of erythromycin on respiratory colonization of *Ureaplasma urealyticum* and the development of chronic lung disease in extremely low birth weight infants. *Pediatr Infect Dis J* 1998;17:615-20.
65. Jonsson B, Rylander M, Faxelius G. *Ureaplasma urealyticum*, erythromycin and respiratory morbidity in high-risk preterm neonates. *Acta Paediatr* 1998;87:1079-84.
66. Lyon AJ, McColm J, Middlemist L, Fergusson S, McIntosh N, Ross PW. Randomized trial of erythromycin on the development of chronic lung disease in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F10-4.
67. Baier RJ, Loggins J, Kruger TE. Failure of erythromycin to eliminate airway colonization with *Ureaplasma urealyticum* in very low birth weight infants. *BMC Pediatr* 2003;3:10.
68. Mhanna MJ, DeLong LJ, Aziz HF. The value of *Ureaplasma urealyticum* tracheal culture and treatment in premature infants following an acute respiratory deterioration. *J Perinatol* 2003;23:541-4.