0031-3998/05/5704-0473
PEDIATRIC RESEARCH
Vol. 57, No. 4, 2005
Printed in U.S.A.
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Intra-Amniotic Infection and Inflammation in Preterm Birth – is Bacteria Always the Connection?

Commentary on the article by Miralles et al. on page 570

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During the last two decades, it has been widely believed that the primary factor contributing to spontaneous preterm birth is vaginal bacteria, which upon ascending into the uterus cause a decidual, placental, and amniotic infection that prompts a fetal inflammatory response (1, 2). Support for this hypothesis has come from studies documenting an association between preterm labor and preterm prelabor rupture of membranes and the presence of chorioamnionitis at placental examination or by the presence of bacteria in the amniotic fluid or between the membranes (3–5). The presence of bacteria in the amniotic fluid or histologic chorioamnionitis is related to high cytokine levels in the amniotic fluid (1, 5). Some women with signs of intra-amniotic inflammation, such as elevated concentrations of cytokines in their amniotic fluid, do not have documented intra-amniotic infection (6, 7). Women with intra-amniotic inflammation without detectable bacteria in the amniotic fluid are more likely to have bacteria detectable between the membranes than those without intra-amniotic inflammation (3, 4). The ability to delineate between intra-amniotic infection and intra-amniotic inflammation might be due to the lack of a methodology sensitive enough to detect minute amounts of bacteria or the lack of our current understanding as to the possible causes of intra-amniotic inflammation.

Bacterial 16S ribosomal RNA polymerase chain reaction (16S rRNA PCR) techniques, which have been introduced recently, successfully identify bacterial genes even when bacterial cultures are negative. For example, when PCR-based techniques are used *Ureaplasma urealyticum* is positively identified in the amniotic fluid of women with preterm prelabor of membranes more often than when assayed by conventional bacterial culture (8). PCR-based methods have been used successfully to identify other types of bacteria (9). Still it has been questioned whether every case of intra-amniotic inflammation has bacteria in the amniotic fluid or between the membranes that have not been detected by the bacterial methods used.

Received December 20, 2004; accepted January 5, 2005.

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DOI: 10.1203/01.PDR.0000156475.50488.B0

One study using conventional bacterial culture techniques found that women in spontaneous labor at term, have amounts of detectable bacteria in amniotic fluid similar to that of women in preterm labor (10). On the other hand, the levels of amniotic fluid cytokines are lower, and the presence of histologic chorioamnionitis is also less common in term spontaneous birth (11). These observations can be interpreted in several ways. One set of inferences suggests that what discriminates between preterm and term labor is not the presence of bacteria in the amniotic cavity, but rather the responses of the mother and fetus.

The authors of a paper in this issue, Miralles *et al.* have studied intra-amniotic infection and inflammation (12). They analyzed both maternal and fetal tissues/fluids of a limited number of patients from various subgroups of preterm birth. 16S rRNA PCR technique and enzyme linked immuno assay for IL-6 and IL-8 were used to analyze placentas, membranes, amniotic fluid, gastric fluid, bronchoalveolar lavage and umbilical cord blood. Their findings suggest that the intra-amniotic milieu before birth can be studied postnatally in gastric fluid (compartment #1) and bronchoalveolar lavage (compartment #2) of the newborn as well as in the amniotic fluid (compartment #3). In addition, the relationship between PCR positivity in each compartment and histologic chorioamnionitis is evaluated. All cases with histologic chorioamnionitis had a positive 16s rRNA PCR from one of the three compartments. All 8 children from pregnancies with histologic chorioamnionitis whose gastric fluid was available had 16S rRNA identified in the gastric fluid. The authors also found a clear relationship between the inflammatory response, measured as IL-6 and IL-8 levels, in various intrauterine compartments to the presence of a positive test for 16s rRNA bacterial gene.

The findings of Miralles *et al.* are important from several points of view (12). Gastric fluid appears to be able to serve as a source of information about neonatal exposure to bacteria *in utero*. When amniocentesis has not been performed, sampling of the gastric fluid might provide information about the intra-amniotic environment. The value of gastric fluid assessment needs to be addressed in a prospective study with a greater number of patients where both compartments are sampled.

The authors report that 70% and 80% of deliveries after preterm prelabor rupture of membranes and preterm labor are

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associated with microbial rDNA. This is not as high as in one recent study (13), but is higher than the 40–50% cited in a recent review (14). Much of the variability probably reflects the entry criteria for study (preterm birth, preterm labor, preterm labor or prelabor preterm membrane rupture, chorioamnionitis, etc.).

Not all pregnancies with presumed inflammation have identifiable bacteria. This begs the question, if bacteria were never truly present, what is the inflammatory stimulus? New experimental data from mice suggest that augmented production of surfactant protein A by the fetal lung near term causes activation and migration of fetal amniotic fluid macrophages to the maternal uterus, where increased production of interleukine-1 beta activates nuclear factor-kappa B, leading to labor (15). If this observation holds true and is the same in humans, it suggests that delivery can start as an intra-amniotic inflammation without any infectious agent triggering the process. Miralles *et al.* also found cases (2/10) of spontaneous preterm labor where no bacteria were found in any of the intrauterine compartments which might indicate a nonbacterial etiology for the initiation of labor and delivery in those cases (12). Another possible explanation to cases of spontaneous preterm labor where bacteria are not detected is that viruses could be playing a more important role than previously thought by activating macrophages *via* the Toll-like receptors (16) and might spread light over the discussion of intra-amniotic infection and inflammation.

REFERENCES

1. Romero R, Mazor M 1988 Infection and preterm labor. Clin Obstet Gynecol 31:553–584
2. Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM 1998 The fetal inflammatory response syndrome. Am J Obstet Gynecol 179:194–202
3. Jacobsson B, Mattsby-Baltzer I, Hagberg H 2005 Interleukin-6 and interleukin-8 in cervical and amniotic fluid: relationship to microbial invasion of the chorioamniotic membranes. BJOG, in press; DOI:10.1111/j.1471-0528.2005.2536x
4. Andrews WW, Hauth JC, Goldenberg RL, Gomez R, Romero R, Cassell GH 1995 Amniotic fluid interleukin-6: correlation with upper genital tract microbial colonization and gestational age in women delivered after spontaneous labor versus indicated delivery. Am J Obstet Gynecol 173:606–612
5. Hillier SL, Witkin SS, Krohn MA, Watts DH, Kiviat NB, Eschenbach DA 1993 The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol 81:941–948
6. Yoon BH, Romero R, Moon JB, Shim SS, Kim M, Kim G, Jun JK 2001 Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. Am J Obstet Gynecol 185:1130–1136
7. Jacobsson B, Mattsby-Baltzer I, Andersch B, Bokstrom H, Holst RM, Wennerholm UB, Hagberg H 2003 Microbial invasion and cytokine response in amniotic fluid in a Swedish population of women in preterm labor. Acta Obstet Gynecol Scand 82:120–128
8. Yoon BH, Romero R, Kim M, Kim EC, Kim T, Park JS, Jun JK 2000 Clinical implications of detection of Ureaplasma urealyticum in the amniotic cavity with the polymerase chain reaction. Am J Obstet Gynecol 183:1130–1137
9. Markenson GR, Martin RK, Tillotson-Criss M, Foley KS, Stewart RS Jr., Yancey M 1997 The use of the polymerase chain reaction to detect bacteria in amniotic fluid in pregnancies complicated by preterm labor. Am J Obstet Gynecol 177:1471–1477
10. Romero R, Nores J, Mazor M, Sepulveda W, Oyarzun E, Parra M, Insunza A, Montiel F, Behnke E, Cassell GH 1993 Microbial invasion of the amniotic cavity during term labor. Prevalence and clinical significance. J Reprod Med 38:543–548
11. Yoon BH, Romero R, Moon J, Chaiworapongsa T, Espinoza J, Kim YM, Edwin S, Kim JC, Camacho N, Bujold E, Gomez R 2003 Differences in the fetal interleukin-6 response to microbial invasion of the amniotic cavity between term and preterm gestation. J Matern Fetal Neonatal Med 13:32–38
12. Miralles R, Hodge R, McParland PC, Field DJ, Bell SC, Taylor DJ, Grant WD, Kotecha S 2005 Relationship between antenatal inflammation and antenatal infection identified by detection of microbial genes by polymerase chain reaction. Pediatr Res 57:570–577
13. Sullivan MH, Steel J, Kennea N, Feldman R, Edwards AD 2004 The role of intrauterine bacteria in brain injury. Acta Paediatr Suppl 93:4–5
14. Le Bouar G, Lassel L, Poulain P 2002 [Markers of infection and inflammation in the amniotic fluid: therapeutic contribution of amniocentesis]. J Gynecol Obstet Biol Reprod (Paris) 31:S52–S56
15. Condon JC, Jeyasuria P, Faust JM, Mendelson CR 2004 Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition. Proc Natl Acad Sci USA 101:4978–4983
16. Sato A, Iwasaki A 2004 Induction of antiviral immunity requires Toll-like receptor signaling in both stromal and dendritic cell compartments. Proc Natl Acad Sci USA 101:16274–16279

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