The Fetal Inflammatory Response Syndrome and Associated Infant Morbidity

Ilan Arad MD and Zivanit Ergaz MD

Department of Neonatology, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel

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In recent years a plethora of studies has confirmed the association of intrauterine infection and inflammation with preterm labor and delivery. More than 40% of all preterm births have been estimated to occur in mothers who have an intrauterine infection, which is largely subclinical. The lower the gestational age at delivery, the greater the frequency of intrauterine infection [1–3]. Microbial invasion of the amniotic cavity is present in about 10% of women with preterm labor and intact membranes and in 30% of patients with preterm premature rupture of membranes. Moreover, bacterial markers have been detected in the amniotic fluid of as many as 60% of patients with preterm labor and intact membranes [4]. Ascending infection from the vagina and cervix is considered to be the most common pathway of intrauterine infection. Less common are the hematogenous dissemination through the placenta, the retrograde seeding from the peritoneal cavity through the fallopian tubes, and the accidental introduction of infection during invasive procedures like amniocentesis [3]. The first stage of ascending infection involves the change and replacement of the normal vaginal and cervical flora by pathologic organisms. Subsequently, invasion and proliferation in the decidua occur, followed by the development of chorioamnionitis and/or fetal vasculitis. Finally, bacteria and/or their products may gain access to the fetus directly from the amniotic fluid (lungs) or through the fetal vessels [3]. It has been suggested that the interaction between the intrauterine milieu and microbes and their products initiates cytokine production and release of prostaglandin that are required for cervical ripening and activation of the myometrium, resulting in premature parturition [5]. Support for the hypothesis that a subclinical intrauterine infection is a cause for preterm delivery is based on the association of lower genital infections, histologic chorioamnionitis, and increased frequency of maternal and neonatal infection, with preterm delivery. Also, bacteria and other markers of infection are often detected in the amniotic fluid prior to preterm labor and delivery with or without rupture of membranes, and prolongation of pregnancy has been achieved following the administration of antibiotics to women with preterm labor and premature rupture of membranes. Furthermore, the introduction of bacteria or bacterial byproducts into the amniotic cavity of several animal species has induced abortion or preterm delivery that could be prevented by prior administration of antibiotics [2].

The intensity and spread of the intrauterine reaction to infection, graded by histologic findings, was found to correlate with intraamniotic and cord blood cytokine levels and with illness severity of the newborn [4,6]. The most advanced reaction to infection was found when fetal participation in the inflammatory process was evidenced by histologic and biochemical criteria [4,7]. The fetal reaction was designated the Fetal Inflammatory Response Syndrome. Cord blood interleukin 6 levels $\geqslant$ 11 pg/ml and the finding of inflammation of the umbilical cord vessels (funisitis) were established as indicators of the fetal reaction to intrauterine infection [4,8].

Fetal inflammatory response syndrome and the lung

Consequent to earlier studies reporting on the association between preterm premature rupture of membranes and a reduced incidence of respiratory distress syndrome, it was widely believed that premature prolonged rupture of the membranes might serve as a stressful stimulus to the fetus, inducing the enhancement of pulmonary maturation through the increase of cortisol production [9]. Though disputed by others [10], some support for the validity of the earlier findings was lent by more recent animal studies demonstrating a significant acceleration of lung maturation following chorioamnionitis caused by intraamniotic endotoxin

Intrauterine infection and inflammation, mostly subclinical, is a frequent cause of preterm labor and delivery

[11]. An increase in surfactant production together with improved lung compliance was demonstrated concomitantly with fetal and neonatal inflammatory reaction but with no increase in cortisol levels. It is conceivable, therefore, that the previously reported association between PPROM and a decreased incidence of respiratory distress syndrome was mediated, at least in part, through the fetal inflammatory response to a subclinical infection. Watterberg et al. [12] studied infants with a birth weight less than 2,000 grams and found an association of histologic chorioamnionitis with less acute lung disease but a higher incidence of chronic lung disease and the presence of IL-1β in tracheal fluid on day 1 of

PPROM = preterm premature rupture of membranes
IL = interleukin

intubation. Support for the role of intrauterine infection in the pathogenesis of chronic lung disease of prematurity has been forwarded by further findings: *Ureaplasma urealyticum*, commonly present in the lower genital tract, has been isolated more frequently in tracheal aspirates taken on day 1 of life from very premature infants who later developed chronic lung disease than in those who were unaffected [13]. This association between Ureaplasma colonization and subsequent development of bronchopulmonary dysplasia was evident prior to and during the surfactant era [14]. An increased incidence of chronic lung disease was found in subsets of premature infants who were exposed to pro-inflammatory cytokines in the amniotic fluid or who had elevated IL-6 cord blood levels at birth [15], suggesting that the trigger for the development of chronic lung disease may commence prior to birth and is associated with a fetal inflammatory response. Also, intrauterine inflammation of the fetal lung, characterized by marked infiltration of neutrophils and macrophages as well as an increase in the expression of IL-8 mRNA in lung tissue, was found to be associated with chorioamnionitis [16].

The initial reports on bronchopulmonary dysplasia related to infants who suffered from severe respiratory distress syndrome and developed chronic lung disease following exposure to high pressure ventilation and oxygen. In recent years, infants of younger gestational age who are rescued often require only mild to moderate ventilatory support secondary to the advent of antenatal steroids, surfactant administration and modern strategies of mechanical ventilation. However, despite the milder initial course, the incidence of chronic lung disease of prematurity has not declined. It was thus suggested that whereas in the past, bronchopulmonary dysplasia was caused mainly by barotrauma and oxygen toxicity, recent cases are more pathognomonic of lung maldevelopment often occurring secondary to the exposure to intrauterine infection and the consequent fetal inflammatory reaction [12,14].

Fetal inflammatory response syndrome and the central nervous system

Very low birth weight infants are at an increased risk for developing cranial ultrasonographic abnormalities during the neonatal period and constitute a considerable proportion of all new cases of cerebral palsy [17]. The sonographic images that best predict later motor and cognitive disabilities are lesions of the cerebral white matter, mainly echo-lucent foci in the paraventricular white matter identified as periventricular leukomalacia [18,19].

Several studies have presented evidence supporting a role for intrauterine infection in the pathogenesis of neonatal intraventricular hemorrhage and white matter damage [20,21]. In a study of 745 low birth weight infants, clinical chorioamnionitis was associated with both the increase in the incidence ($P < 0.005$) and the severity ($P < 0.007$) of the cerebral lesions [20]. The presence of intrauterine infection has also been identified as an important risk factor for cerebral palsy in very low birth weight infants [22,23]. Though earlier analyses failed to establish such an association in term infants [24], recent work presented evidence that chorioamnionitis is an independent risk factor for cerebral palsy also among term and near-term infants [25]. Adinolfi [26] proposed that cytokines produced by the immune system during the course of maternal infection are harmful to the developing fetal brain. Leviton [27] extended the hypothesis, suggesting that inflammatory cytokines released during the course of an intrauterine infection may induce cerebral white matter lesions with subsequent development of cerebral palsy. Subsequently, it was demonstrated that elevated levels of inflammatory cytokines in the amniotic fluid (IL-6, IL-1β and tumor necrosis factor-alpha) and in cord blood (IL-6) predict the evolvement of neonatal cerebral lesions detected by sonography [28,29]. Duggan and colleagues [30] utilized magnetic resonance imaging very soon after the delivery of 50 infants born after 23–29 weeks of gestation to detect cerebral lesions, and demonstrated an activation of intrauterine T cells and increased levels of cord blood pro-inflammatory cytokines in those infants with lesions. These results suggest that the increase in cytokine levels occurred as a result of prenatal exposure to an antigen rather than hypoxia, brain injury or parturition [30]. In line with the assumption that the fetal inflammatory reaction, but not the maternal or intrauterine infection per se, is damaging to the brain is the association of fetal vasculitis, but not chorioamnionitis, with echo-lucent lesions [31].

The hypothesis presented by Leviton in 1993 [27] required the proof of an association between determinants of the fetal inflammatory response and subsequent development of cerebral palsy. Yoon et al. [32] examined the association of funisitis and amniotic fluid cytokine levels with the development of cerebral palsy at the age of 3 years in a cohort of 123 prematurely born children. After adjustment for gestational age at birth, the presence of funisitis and elevated concentrations of IL-6 and 8 in amniotic fluid significantly increased the odds for the development of cerebral palsy (odds ratios 5.5, 6.4, 5.9, respectively, $P < 0.05$ for each). Similarly, Mittendorf and co-workers [33] demonstrated the association of funisitis and elevated IL-6 cord blood levels with impaired neurologic outcome at age 18 months.

The fetal inflammatory participation in these events harbors subsequent neurologic and pulmonary impairments

The specific mechanism by which cerebral abnormalities are induced through intrauterine infection and the consequent fetal inflammatory response has not yet been completely clarified. It has been suggested [34] that microorganisms or microbial products gaining access to the fetus can stimulate mononuclear cells to produce IL-1 and TNF. These cytokines can increase the permeability of the blood-brain barrier and facilitate the passage of

TNF = tumor necrosis factor

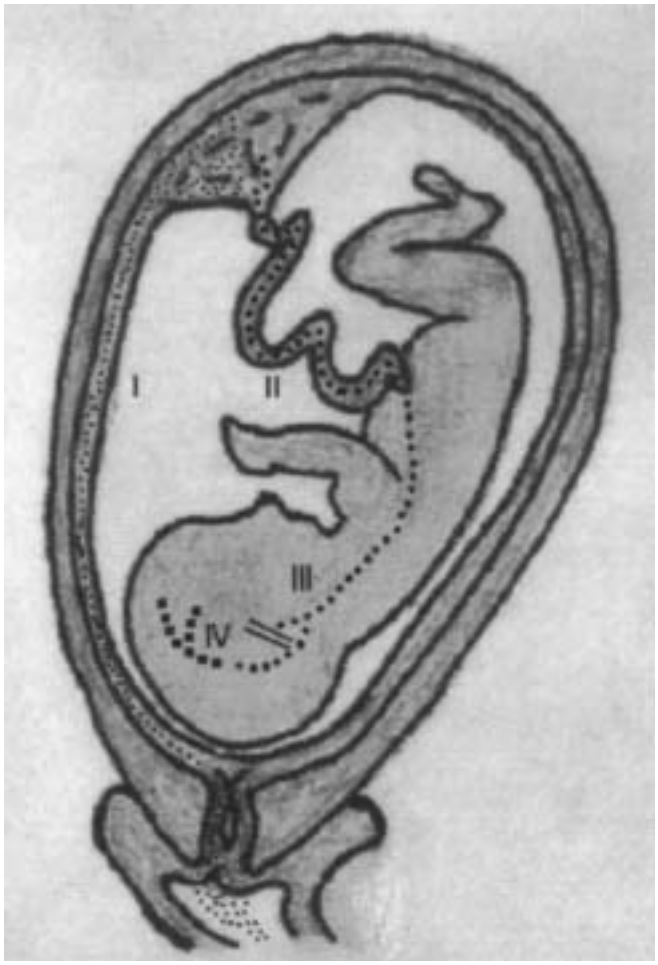

Figure 1. Suggested pathways of the Fetal Inflammatory Response causing cerebral damage.
I – Intrauterine ascending infection initiating placental and fetal inflammatory response. II – Fetal cytokines in the fetal circulation. III – Cytokines alter blood-brain barrier permeability and gain access into the central nervous system. IV – These cytokines may cause brain damage directly and/or through the induction of further cytokine production by microglia and proliferating astrocytes.

cytokines and microbial products into the central nervous system, inducing the production of IL-1 and TNF by fetal microglia. These, in turn, activate the proliferation of astrocytes and further production of TNF, causing damage in the oligodendrocyte, the cell responsible for the deposition of myelin [Figure 1]. Cytokines were demonstrated in both the fetal circulation and the brain during and following intrauterine infection, and their ability to modulate blood-brain barrier permeability, penetrate into the brain and cause endothelial damage with subsequent germinal matrix hemorrhage, suggests their significant role in the pathogenesis of intraventricular hemorrhage and white matter damage.

Prevention and implications

The association between antenatal intrauterine infection and preterm labor and neonatal complications has led to attempts to prevent or suppress the infection. Though prolongation of pregnancy through the administration of antibiotics has been achieved in the case of PPROM, evidence to support amelioration of the fetal inflammatory response in other instances of early parturition is still lacking [2]. Antenatal exposure to exogenous corticosteroids has been repeatedly shown to reduce the incidence and severity of intraventricular hemorrhage and white matter damage [35] and may be protective against chronic lung disease of prematurity [36]. Dammann and Leviton [37,38] have suggested that trophic agents such as oligotrophins that promote growth and maturation of cerebral oligodendrocytes, and biological response modifiers (anti-inflammatory cytokines, cytokine binding proteins, cytokine receptor blockers), may protect against white matter injury. Suggestions for the role of micronutrients such as vitamin C and vitamin E in the protection against neonatal injury caused by antenatal inflammation await confirmation by further studies [3], as does the research of genetic factors contributing to increased fetal susceptibility to infection and inflammation [39].

Further studies are required to establish preventive strategies

The association between intrauterine infection and subsequent infant neurologic and pulmonary ailments has been substantiated by human and experimental studies. A recent experimental study in mice produced evidence that cardiovascular compromise may also be induced by the fetal inflammatory response [40]. It is suggested that indicators of the fetal inflammatory response syndrome – such as elevated levels of cord blood IL-6 or the presence of funisitis – be routinely examined in cases of preterm birth. Such data may not only enhance our understanding of the pathophysiology of the inflammatory process and the development of preventive strategies, but also harbor prognostic and medico-legal implications.

References

1. Hillier S, Nugent R, Eschenbach D, et al. The association between bacterial vaginosis and a preterm delivery of a low birth weight infant. The Vaginal Infections and Prematurely Study Group. *N Engl J Med* 1995;33:1737–42.
2. Guinn D, Gibbs R. Infection related preterm birth: a review of the evidence [Review]. *NewRev* 2002;3 (5):e86–95.
3. Romero R, Chaiworapongsa T, Espinoza J. Micronutrients and intrauterine infection, preterm birth and the fetal inflammatory response syndrome [Review]. *J Nutr* 2003;133:1668–73S.
4. 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.
5. Kelly RW. Inflammatory mediators and parturition [Review]. *Rev Reprod* 1996;1:89–96.
6. Negishi H, Yamada H, Mikuni M, et al. Correlation between cytokine levels of amniotic fluid and histological chorioamnionitis in preterm delivery. *J Perinat Med* 1996;24:633–9.
7. Nacccasha N, Hinson R, Montag A, Ismail M, Bintz L, Mittendorf R. Association between funisitis and elevated interleukin-6 in cord blood. *Obstet Gynecol* 2001;97:220–4.
8. Pacora P, Chaiworapongsa T, Maymon E, et al. Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflammatory response syndrome. *J Matern Fetal Med* 2002;11:18–25.

9. Berkowitz RL, Kantor RD, Beck GJ, Warshaw JB. The relationship between rupture of membranes and the respiratory distress syndrome: an update and plan of management. *Am J Obstet Gynecol* 1978;131:503–8.
10. Jones MD, Burd LI, Bowes WA, Battaglia FC, Lubchenco LO. Failure of the association of premature rupture of membranes with respiratory distress syndrome. *N Engl J Med* 1975;292:1253–7.
11. Kramer BW, Moss TJ, Willet KE, et al. Dose and time response after intraamniotic endotoxin in preterm lambs. *Am J Respir Crit Care Med* 2001;164:982–8.
12. Watterberg KL, Demers LM, Scott SM, Murphy S. Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops. *Pediatrics* 1996;97:210–15.
13. Cassel 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;ii:240–5.
14. Lyon A. Chronic lung disease of prematurity. The role of intra-uterine infection [Review]. *Eur J Pediatr* 2000;159:798–802.
15. Yoon BH, Romero R, Kim KS, et al. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. *Am J Obstet Gynecol* 2001;181:773–9.
16. Schmidt B, Cao L, Mackensen-Haen S, Kendziorra H, Klingel K, Speer CP. Chorioamnionitis and inflammation of the fetal lung. *Am J Obstet Gynecol* 2001;185:173–7.
17. Bhushan V, Paneth N, Kiely JL. Impact of improved survival of very low birth weight infants on recent secular trends in the prevalence of cerebral palsy [Review]. *Pediatrics* 1993;91:1094–100.
18. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and non-disabling cerebral palsy at age two in low birth weight population. *Pediatrics* 1995;95:249–55.
19. Leviton A, Paneth N. White matter damage in preterm newborns – an epidemiologic perspective [Review]. *Early Hum Dev* 1990;24:1–22.
20. Verma U, Tejani N, Klein S, et al. Obstetric antecedents of intraventricular hemorrhage and periventricular leukomalacia in the low-birth-weight neonate. *Am J Obstet Gynecol* 1997;176:275–81.
21. Hansen A, Leviton A. Labor and delivery characteristics and risks of cranial ultrasonographic abnormalities among very-low-birth-weight infants. *Am J Obstet Gynecol* 1999;181:997–1006.
22. Murphy DJ, Sellers S, Mackenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. *Lancet* 1995;346:1449–54.
23. O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. *Paediatr Perinat Epidemiol* 1998;12:72–83.
24. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 1986;315:81–6.
25. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA* 2003;290:2677–84.
26. Adinolfi M. Infectious disease in pregnancy, cytokines and neurological impairment: an hypothesis [Review]. *Dev Med Child Neurol* 1993;35:549–53.
27. Leviton A. Preterm birth and cerebral palsy: is tumor necrosis factor the missing link? [Review]. *Dev Med Child Neurol* 1993;35:553–8.
28. Yoon BH, Jun JK, Romero R, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1β and tumor necrosis factor-α), neonatal brain white matter lesions, and cerebral palsy. *Am J Obstet Gynecol* 1997;177:19–26.
29. 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.
30. Duggan PJ, Maalouf EF, Watts TL, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001;358:1699–700.
31. Leviton A, Paneth N, Reuss ML, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. *Pediatr Res* 1999;46:566–75.
32. 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.
33. Mittendorf R, Montag AJ, MacMillan W, et al. Components of the systemic fetal inflammatory response syndrome as predictors of impaired neurologic outcomes in children. *Am J Obstet Gynecol* 2003; 188:1438–46.
34. Yoon BH, Park CW, Chaiworapongsa T. Intrauterine infection and the development of cerebral palsy [Review]. *Br J Obstet Gynaecol* 2003;110 (Suppl 20):124–7.
35. Arad I, Bromiker R. Developmental assessment prematurely born children exposed to antenatal corticosteroids [Review]. *IMAJ* 2003; 5:659–61.
36. Van Marter LJ, Leviton A, Kuban KC, Pagano M, Allred EN. Maternal glucocorticoid therapy and reduced risk of bronchopulmonary dysplasia. *Pediatrics* 1990;86:331–6.
37. Dammann O, Leviton A. Brain damage in preterm newborns: might enhancement of developmentally regulated endogenous protection open a door for prevention? [Review]. *Pediatrics* 1999;104:541–50.
38. Dammann O, Leviton A. Brain damage in preterm newborns: biological response modification as a strategy to reduce disabilities [Review]. *J Pediatr* 2000;136:433–8.
39. Dammann O, Leviton A. Role of the fetus in perinatal infection and neonatal brain damage [Review]. *Curr Opin Pediatr* 2000;12:99–104.
40. Rounioja S, Rasanen J, Glumoff V, Ojaniemi M, Makikallio K, Hallman M. Intra-amniotic lipopolysaccharide leads to fetal cardiac dysfunction. A mouse model for fetal inflammatory response. *Cardiovasc Res* 2003;60: 156–64.

Correspondence: Dr. I. Arad, Dept. of Neonatology, Hadassah University Hospital, Mt. Scopus, Jerusalem 91240, Israel.
Phone: (972-2) 587-4432
Fax: (972-2) 581-3068
email: arad@hadassah.org.il

Capsule

No nausea in acute renal colic

A systematic review was performed to compare treatment with opioids versus non-steroidal anti-inflammatory drugs (NSAIDs) in patients with acute renal colic. Overall, data analysis of 20 randomized controlled trials showed that NSAIDs achieve slightly better pain relief, reduce the need for further analgesia following the first treatment, and cause less vomiting than opioids. The writers conclude that NSAIDs should be the first-line analgesics in patients with acute renal colic.

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