The Fetal Inflammatory Response Syndrome and Associated Infant Morbidity

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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 > 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.PPRON = preterm premature rupture of membranes

IL = Interleukin

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. Wattenberg 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
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 periventricular 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 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 IL-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 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

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

TNF = tumor necrosis factor
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 oligodendrocytes 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 funisis – 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 medicolegal implications.

References


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**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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