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Intrauterine Infection and Preterm Labor

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ABSTRACT

Preterm birth remains the leading cause of perinatal mortality and morbidity. Evidence suggests that intrauterine infection plays an important role in the pathogenesis of preterm labor. This article reviews the clinical data supporting this theory and the cellular and biochemical mechanisms by which intrauterine infection may initiate uterine contractions. The clinical and laboratory methods of diagnosing clinical chorioamnionitis and asymptomatic bacterial invasion of the intraamniotic cavity are also reviewed. Finally, the management of clinical chorioamnionitis and asymptomatic microbial invasion of the amniotic fluid and the use of adjunctive antibiotic therapy in the treatment of preterm labor are presented. © 1995 Wiley-Liss, Inc.

KEY WORDS

Chorioamnionitis, microbial invasion of the amniotic cavity, pregnancy

Preterm birth remains the leading cause of perinatal mortality and morbidity. Eighty-three percent of the neonatal mortality in nonanomalous infants occurs in infants born before the 37th week of gestation.[1] Premature infants who survive the perinatal period experience significant morbidity including respiratory distress, intraventricular hemorrhage, sepsis, necrotizing enterocolitis, and patent ductus arteriosus.[2] Despite the well-recognized risks of preterm birth and concerted efforts to successfully arrest preterm labor, the incidence of preterm delivery has not decreased over the past decade, remaining at 9.6%.[3]

Recent research focusing on the pathogenesis of preterm labor suggests that intrauterine infection may play an important role in preterm labor and delivery. This article reviews the clinical, cellular, and biochemical data that support this theory, as well as the clinical and laboratory methods of diagnosing clinical chorioamnionitis and asymptomatic bacterial invasion of the intraamniotic cavity. Finally, the management issues regarding the treatment and role of adjunctive antibiotic therapy in preterm labor are presented.

The term "intrauterine infection" includes both clinical and asymptomatic microbial invasion of the amniotic cavity. For the purpose of this review "histologic chorioamnionitis" is defined as histologic inflammation of the amnion and chorion and "clinical chorioamnionitis" is reserved for the clinical syndrome associated with microbial invasion of the intraamniotic cavity.

INTRAUTERINE INFECTION AND PRETERM DELIVERY

Clinical Evidence

A review of 15 studies in which amniocenteses were performed on women in preterm labor with intact membranes reveals the rate of microbial invasion of the amniotic cavity to be 12.2%.[4–18] The bacterial isolation rates range from 0 to 48%, depending on the study population and culture technique. Although most of these women had no signs or symptoms of infection at the time of presentation, they

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were more likely to develop clinical chorioamnionitis. Furthermore, women in preterm labor with positive cultures were more likely to be refractory to tocolytics and to have spontaneous premature rupture of the membranes (PROM) and a shorter interval from presentation to delivery. This evidence indirectly supports the role of infection in the pathogenesis of preterm labor with intact membranes. Alternatively, these data could be interpreted to suggest that women with preterm labor are at increased risk for microbial invasion of the amniotic cavity.

PROM accounts for up to one-third of all preterm deliveries. Seven studies have examined the rate of intrauterine infection by performing transabdominal amniocentesis on women with PROM.[19–25] Transabdominal amniocenteses were successfully performed on 59% of these women, 28% of whom had positive amniotic fluid cultures. The rate of microbial invasion of the amniotic cavity in the women with unsuccessful amniocenteses is unknown but theoretically higher than 28%, as women with PROM and oligohydramnios are more likely to develop chorioamnionitis[23,26] but less likely to have a successful amniocentesis due to technical difficulty.[19–25] Therefore, these studies support the association of intrauterine infection and PROM, although a causal relationship has not been clearly established. One study documented a higher incidence of positive cultures in women who presented with PROM and preterm labor (39%) compared with women with PROM alone (25%).[25] Eighty-one of 160 women with negative cultures who were not in labor at the time of admission subsequently developed preterm labor. Of these 81 women, 48 had repeat amniocenteses at the onset of labor, and 75% had positive cultures at that time.[25] This suggests that intrauterine infection may play a pivotal role in the onset of preterm labor associated with PROM.

Preterm delivery is associated with an increased rate of postpartum endometritis and early neonatal sepsis,[27–29] which provides further circumstantial evidence to support intrauterine infection as an etiological factor in preterm labor and delivery.

The pathologic examination of the placenta and membranes revealed an increased rate of histologic chorioamnionitis following premature delivery (up to 60%) compared with the rate following term delivery (up to 20%).[30,31] As histologic chorioamnionitis is correlated with positive amniotic-fluid cultures, the hypothesis is that intrauterine infection, with resulting inflammation of the placental membranes, stimulates the onset of preterm labor.

The pathogenesis of intrauterine infection appears to be related to ascending pathogens. An association between genitourinary colonization with group B streptococcus[32,33] and *Neisserisa gonorrhoeae*[34–36] and premature delivery has been established. In addition, the eradication of these pathogens with antibiotics has significantly decreased the preterm delivery rate.[37,38] Bacterial vaginosis and cervicovaginal colonization with *Bacteroides fragilis* have also been associated with preterm delivery, although their eradication has yet to demonstrate a significant benefit.[31,39–44] The role of cervicovaginal *Chlamydia trachomatis, Ureaplasma urealyticum,* and *Trichomonas vaginalis* on prematurity is less well established.

Biochemical Mechanisms

Prostaglandins have been implicated in the initiation of labor at term. This theory is supported by the observations that 1) prostaglandins and their precursor, arachidonic acid, stimulate abortion and labor;[45] 2) amniotic-fluid levels of prostaglandins and arachidonic acid increase during labor;[46–49] and 3) prostaglandin inhibitors arrest preterm contractions and delay the onset of labor at term.[50–52] The role of prostaglandins in the onset of preterm labor is less well defined. However, women with preterm labor and microbial invasion of the amniotic cavity have higher amniotic fluid levels of PGE_2 and $PGF_{2\alpha}$ than women with preterm labor and negative amniotic-fluid cultures or women without preterm labor.[53–58] The sources of these prostaglandins are postulated to be the amnion, chorion, and decidua.[59–61] Indeed, media from bacterial cultures stimulate PGE_2 and $PGF_{2\alpha}$ production from isolated human amnion and decidual cells.[62–65] Therefore, prostaglandins appear to play an important role in preterm labor in the presence of infection.

Prostaglandin production from placental membranes and decidual cells increases directly in response to bacterial products such as phospholipase A_2 and phospholipase C. These stimulate the release of arachidonic acid from the membrane phospholip-

ids, phosphatidylinositol and phosphatidylethanolamine.[66–68] Endotoxin, or lipopolysaccharide, a component of the cell wall of gram-negative bacteria, stimulates prostaglandin production by the amnion and decidua[69,70] and is increased in the amniotic fluid of women with microbial invasion of the amniotic cavity[71] or PROM and labor.[72] However, the amount of endotoxin found in the amniotic cavity in women with PROM and labor[72] is lower than that required to stimulate prostaglandin production by the amnion.[69] Therefore, it has been postulated that an amplification of the host response by endotoxin stimulates the production of inflammatory mediators.

Endotoxin stimulates the production of inflammatory mediators, cytokines or monokines, from macrophages.[73–76] The 3 cytokines that have been extensively investigated in relation to preterm labor and intrauterine infection are interleukin-1, interleukin-6, and tumor-necrosis factor. These cytokines stimulate the production of prostaglandins by the amnion, chorion, decidua, and myometrium in vitro.[73,75,77–81] The amniotic-fluid levels of interleukin-1, interleukin-6, and tumor-necrosis factor are higher in women with microbial invasion of the amniotic cavity and preterm labor compared with the levels in women with microbial invasion of the amniotic cavity who are not in labor or women without microbial invasion of the amniotic cavity.[73,75,77–81] Elevated cytokine levels are also associated with increased amniotic-fluid levels of prostaglandins and unsuccessful tocolysis.[75,82–84] Finally, the systemic administration of interleukin-1 in mice induces preterm delivery,[85] which can be inhibited by the administration of a natural interleukin-1 receptor antagonist.[86] The amniotic-fluid levels of interleukin-1 receptor antagonist are reduced in women with intraamniotic-fluid infection and preterm labor despite elevated levels of interleukin-1.[87]

The sum of these data suggests that microbial invasion of the amniotic cavity results in a release of bacterial endotoxin which stimulates cytokine production and results in arachidonic-acid metabolism, prostaglandin production, and the onset of labor. However, the simultaneous or sequential production of several cytokines may be necessary to stimulate this cascade through a positive feedback mechanism[88,89] or a prolonged exposure to elevated levels of cytokines may be necessary, as individual cytokines do not acutely stimulate myometrial contractile activity in vitro.[90]

DIAGNOSIS OF INTRAUTERINE INFECTION

A diagnosis of clinical chorioamnionitis is based upon fever >37.8°C; rupture of membranes; and 2 or more of the following criteria: maternal or fetal tachycardia, uterine tenderness, malodorous amniotic fluid, or peripheral leukocytosis with no other site of infection.[91,92]

The gold standard for the diagnosis of subclinical intrauterine infection has been the amniotic-fluid culture. Because the results are usually not obtainable for 48–72 h, several techniques for the rapid identification of microbial invasion of the amniotic cavity have been investigated.

A Gram's stain of the amniotic fluid is a simple and inexpensive test to perform. Numerous reports have shown it to have a sensitivity of about 49.5% (140/283 patients) and a specificity of 97.7% (888/909 patients) when compared with the amniotic-fluid culture in the setting of preterm labor with intact membranes or PROM.[4,5,8,11,13,16,19–22,24,93–97] The low sensitivity of the Gram's stain to detect microbial invasion of the amniotic cavity is probably related to its inability to demonstrate mycoplasmas which are among the most common isolates in asymptomatic microbial invasion of the amniotic cavity.[97]

Low amniotic-fluid glucose levels have been investigated as a rapid, simple, and inexpensive indicator of microbial invasion of the amniotic cavity. With a cutoff level of <14–16 mg/dl, this technique has been found to have a sensitivity of 33–92% and a specificity of 58–94% in women with preterm labor or PROM when compared with amniotic-fluid cultures.[94–98] Due to the wide variation in sensitivity and specificity, the clinical utility of amniotic-fluid glucose levels in identifying microbial invasion of the amniotic cavity is low.

An amniotic-fluid white blood cell (WBC) count of ≥ 50 cells/mm^3 has been shown to have a sensitivity of 64% and specificity of 94% when compared with amniotic-fluid culture for identifying microbial invasion of the amniotic cavity in women with preterm labor and intact membranes.[97] The amniotic-fluid WBC count may be useful in women with asymptomatic microbial invasion of the amni-

otic fluid, but otherwise has little clinical value. The leukocyte esterase assay of amniotic fluid (a measure of leukocyte activity) was shown to have a higher sensitivity (81%) in one study,[99] but this report has not been confirmed.[95]

A laboratory technique, currently unavailable for clinical use in most centers, is the determination of amniotic-fluid interleukin-6 levels. Elevated amniotic-fluid interleukin-6 levels have been found to be more predictive of microbial invasion of the amniotic cavity, amniocentesis-to-delivery interval, and neonatal complications than the Gram's stain, glucose concentration, or WBC count in women with preterm labor and intact membranes and in women with PROM.[96,97,100] However, there are no studies documenting a benefit from intervention in the setting of preterm labor or PROM with elevated cytokine levels. Therefore, the clinical relevance of these reports is uncertain.

MANAGEMENT

Clinical Chorioamnionitis

Once the diagnosis of clinical chorioamnionitis has been made, antibiotic therapy should be instituted. Prompt intrapartum treatment clearly decreases the rate of neonatal and maternal morbidity.[101] As chorioamnionitis is a polymicrobial infection, the combination therapy of ampicillin and gentamicin is effective.[101–103] Single-agent therapy using second- or third-generation cephalosporins or extended-spectrum penicillins has not been studied in large randomized trials. A critical diagnosis-to-delivery interval has not been determined; however, there are little data on the outcome in patients who deliver >12 h after diagnosis. It has been recommended that clindamycin be added to the antibiotic regimen if the patient is delivered by cesarean in an attempt to decrease the severity of postpartum endometritis, although little data exist to support this recommendation.[91]

Asymptomatic Microbial Invasion of the Amniotic Fluid

While the early identification of microbial invasion of the amniotic cavity raises the possibility of many innovative therapeutic options, such as antibiotics without prompt delivery or anticytokines, these options have not been investigated. Many patients with preterm labor and microbial invasion of the amniotic cavity are refractory to tocolysis, and women with PROM and microbial invasion of the amniotic cavity have shorter latency periods. The management of a patient with preterm labor or PROM who has a positive amniotic-fluid culture without clinical chorioamnionitis has not been addressed in the literature. In our clinical practice, we do not routinely perform an amniocentesis for an amniotic-fluid culture in a woman with preterm labor or a woman with PROM. However, we recommend an amniotic-fluid culture in the case of refractory preterm labor. In this situation, we initiate antibiotic therapy and proceed toward delivery if the amniotic-fluid culture is positive. Due to the paucity of data in this area, these management decisions should be individualized.

Adjunctive Antibiotic Therapy in Preterm Labor

The large body of evidence that supports an etiologic role of infection in preterm labor has prompted several investigations of adjuvant antibiotics for women with preterm labor. To date, the reported results have been contradictory. McGregor et al.[104] randomized 17 patients to a β-sympathomimetic agent plus placebo or β-sympathomimetic agent plus erythromycin and found a statistically significant increase in the number of women who delivered at term in the erythromycin-treated group. Morales et al.[105] randomized 150 women with "idiopathic preterm labor" to ampicillin, erythromycin, or no treatment. They found a statistically significant prolongation of pregnancy in the antibiotic-treated groups; however, the administration of a placebo was not included in the study design, a wide range was noted in the number of days of prolongation of gestation, and no significant improvement was shown in the proportion of pregnancies reaching 37 weeks gestation. McGregor et al.[106] reported a prolongation of pregnancy (35 vs. 25 days) in 103 women receiving tocolytics for preterm labor who were randomized to receive clindamycin or placebo.

In contrast to these 3 studies, Newton et al.[107] found no difference in the prolongation of pregnancy or outcome in 78 women randomized to receive either ampicillin plus erythromycin or placebo in conjunction with standard tocolytics. They reported similar results in 86 patients receiving magnesium-sulfate tocolysis who were randomized to receive ampicillin-sulbactam plus indomethacin

or placebo.[108] Recently, in a multicenter double-blind, placebo-controlled trial, 277 women on tocolytic therapy for preterm labor were randomized to receive either ampicillin plus erythromycin or placebo.[109] No difference was found in the rate of preterm delivery, clinical chorioamnionitis, endometritis, or neonatal outcome. In this study, only 5.8% of the 239 women who had amniocenteses had positive amniotic-fluid cultures.

Basic and clinical evidence supports the etiologic role of infection in some cases of preterm labor. Intrauterine infection is often present in women with preterm labor or PROM, and bacterial products such as endotoxin and cytokines stimulate prostaglandin production. These data suggest a role for antibiotics in the prevention of preterm birth. As preterm labor is probably multifactorial,[110] it is unlikely that adjunctive antibiotic therapy will be of any therapeutic benefit in those women in whom infection is not present. Clearly, there is a need for a large randomized placebo-controlled study on the effect of adjunctive antibiotic therapy in women in preterm labor and intact membranes with asymptomatic microbial invasion of the amniotic cavity.

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