



Is there a link between cerebral palsy and chorioamnionitis?

Yes This meta-analysis found a significant association between cerebral palsy (CP) and clinical and histologic chorioamnionitis, with a pooled odds ratio (OR) of 2.42 (95% confidence interval [CI], 1.52–3.84) and 1.83 (95% CI, 1.17–2.89), respectively. Other studies strongly suggest that the association is causal.

Shatrov JG, Birch SCM, Lam LT, Quinlivan JA, McIntyre S, Mendz GL. Chorioamnionitis and cerebral palsy: a meta-analysis. Obstet Gynecol. 2010;116(2 Pt 1):387–392.

► EXPERT COMMENTARY

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CP is heterogeneous in both its clinical manifestations and its causation. It is now clear that **no more than 10% of all cases result from intrapartum injury**.^{1–3} The vast majority of cases (>90%) arise from circumstances unrelated to labor. Among the variables associated with CP are antepartum entities such as developmental abnormality, metabolic derangement, genetic disorders, infection or inflammation, antepartum hemorrhage (with or without a recognized coagulation disorder), and autoimmune disease. Even postnatal events within the first few years of life may be implicated, including complications of prematurity or postmaturity, trauma, and infection.

It has long been known from case series, case-control studies, cohort studies, and at least two earlier meta-analyses^{4,5} that a diagnosis of intrauterine infection (chorioamnionitis) during pregnancy—whether made by clinical examination, histologic examination of the placenta, or amniotic fluid culture—is associated with an increased risk of CP. (These data are reviewed in a joint statement by ACOG and the American Academy

of Pediatrics on the pathogenesis of neonatal encephalopathy and CP.²)

This new meta-analysis by Shatrov and colleagues confirms the association between chorioamnionitis and CP. Other than that, it adds little to the existing literature and provides no additional information for clinicians on how to manage high-risk patients.

Inflammation may be the real culprit

The association between intrauterine infection and neurologic injury in offspring (including CP) is almost certainly causal. Using a rabbit model, Yoon and coworkers demonstrated that intrauterine infection leads to white matter lesions in the fetal brain that closely resemble the lesions of infection-associated CP seen in the human infant.⁶ Similar observations have been made in mice and pigs.

The mechanisms underlying these end-organ injuries are not well understood, but the weight of evidence suggests that they are an indirect result of the pro-inflammatory cascade triggered to subdue the infection, rather than a direct effect of the infectious organisms themselves.^{7,8} Therefore, it may be more accurate to refer to an association between CP and intra-amniotic *inflammation* rather than intra-amniotic infection.

Increasing evidence suggests that it is low-grade chronic inflammation that leads to neurologic injury rather than acute infection.^{9,10} Clinicians should find this evidence reassuring because it suggests that we are doing our patients no harm when we recommend, for example, expectant management for ruptured membranes remote from term or induction of labor rather than urgent cesarean in the setting of confirmed intra-amniotic infection.

Can CP be prevented?

A number of interventions have been proposed in an effort to prevent CP, with variable

FAST TRACK

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results. They include selective administration of antenatal corticosteroids or magnesium sulfate, elective cesarean delivery, and neonatal hypothermia therapy. Broad-spectrum antibiotics are routinely administered to women who have intra-amniotic infection, primarily to prevent the spread of infection beyond the uterus. If intrauterine infection is causally related to brain injury, can such antibiotic therapy prevent CP?

There is no evidence that antibiotics can protect against neurologic injury. In fact, antibiotics can be detrimental, according to a recent 7-year follow-up of the ORACLE-II randomized clinical trial, which was designed to investigate the effect of broad-spectrum antibiotics on perinatal outcome in women who have preterm labor and intact membranes.¹¹ In this study, fetuses exposed to broad-spectrum antibiotics had a significantly higher risk of CP at age 7 years, with an adjusted odds ratio (OR) of 1.93 for erythromycin (95% CI, 1.21–3.09) and 1.69 for co-amoxiclav (95% CI, 1.07–2.67). Fetuses randomized to receive both antibiotics had an even higher risk of CP. The incidence of CP was 4.55% among these fetuses, compared with 1.97% among those receiving co-amoxiclav alone, 2.29% for those receiving erythromycin alone, and 1.63% for those randomized to the placebo group.

The mechanism of injury is not clear, but it may be that antibiotics may suppress infection and delay delivery, thereby prolonging the fetus's sojourn in a hostile, pro-inflammatory intrauterine milieu.

If neurologic injury is indeed the result of inflammation rather than infection, then anti-inflammatory agents, such as corticosteroids, cyclooxygenase inhibitors, and N-acetylcysteine—alone or in combination with antibiotics—may prevent neurologic injury in the setting of intrauterine infection. Studies into this possibility are under way, and the results are eagerly awaited. ☺

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although intrauterine infection is almost certainly a cause of CP, the mechanism of injury is likely indirect and a result of the activation of the pro-inflammatory cascade rather than the presence of the infectious organisms themselves. Moreover, it is chronic low-grade inflammation rather than acute infection that seems to be the major culprit.

For these reasons, physicians should not alter current clinical practices such as expectant management for ruptured membranes remote from term, or induction of labor (rather than urgent cesarean) when infection is confirmed. Broad-spectrum antibiotics should be administered in the setting of intra-amniotic infection, with delivery following (primarily to prevent the infection from spreading outside of the uterus), but antibiotic therapy does not appear to prevent neurologic injury and may even be detrimental. Taken together, these data suggest we should maintain the status quo until further studies illuminate more effective alternatives.

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