Maternal Inflammation Linked to Autism in Offspring

Pam Harrison May 13, 2013

DONOSTIA / SAN SEBASTIÁN, Spain — A significant association is being reported between increasing levels of maternal C-reactive protein (CRP) and the risk for autism spectrum disorder (ASD).

"We investigated the association between early gestational CRP, an established inflammatory biomarker, prospectively assayed in maternal sera, and childhood autism in the Finnish Prenatal Study of Autism [FiPS-A], and the analysis revealed elevated maternal CRP during pregnancy is related to an increased risk of autism in offspring," said study investigator Alan Brown, MD, MPH, professor of clinical psychiatry and clinical epidemiology, College of Physicians and Surgeons of Columbia University, New York City.

Dr. Brown reported the findings here at the 12th Annual International Meeting for Autism Research (IMFAR).

Mechanism Unknown

The FiPS-A is a large national birth cohort involving 1.6 million pregnancies. Offspring born in Finland between 1987 and 2005 were followed up until 2007.

Archived serum specimens from the first and early second trimesters were analyzed for the study, and the Finnish Hospital/Outpatient Discharge Registry was used to identify all cases of childhood autism.

A total of 677 children with ASD were matched to control individuals from the same birth cohort.

"There was a greater than 40% increase in the risk of childhood autism following exposure to elevated maternal CPR...in the highest quintile compared to maternal CRP in the lowest quintile," investigators report.

The highest quintile of CRP was defined a priori as a CRP >5.84 mg/dL, compared with a CPR in the lowest quintile of 0.10 - 0.92 mg/dL.

Investigators also observed an 80% increase in the risk for childhood ASD following exposure to elevated CPR in the highest decile compared with the lowest decile. The highest decile CPR was again defined a priori as a CRP >9.55 mg/dL; the lowest decile CRP was defined as a CRP of 0.10 - 0.57 mg/dL.

The reported risk between elevated quintiles and deciles of maternal CRP and ASD is similar to most other potential autism risk factors.

Researchers also noted associations between maternal CRP and the risk for ASD in both sexes, although the association was numerically greater for females. However, the association between increasing maternal CRP and both sexes fell short of statistical significance.

"The molecular mechanisms [between elevated CRP and ASD risk] are not known," Dr. Brown told *Medscape Medical News*. "But they could involve inflammation in the fetus and consequent effects on fetal brain development by activating immune cells in the fetal brain and altering the way the brain develops."

Investigators are next planning to study infections during pregnancy as well as other risk factors associated with maternal inflammation. Infections have been associated with increased maternal inflammation, as indexed by CRP.

Meanwhile, Dr. Brown cautioned that women should not take nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy to reduce inflammatory risk.

"We don't know whether or not NSAIDs are safe to take during pregnancy," Dr. Brown emphasized. "I would not recommend that mothers do this because of our study."

NSAIDs Not Recommended

In a separate study, Tina Tseng, PhD, assistant professor of public health, Campbell University College of Pharmacy and Health Sciences, Buies Creek, North Carolina, did find that mothers of children with autism were 35% less likely than those with typically developing children to report having taken NSAIDs around the period of conception or during pregnancy (odds ratio [OR], 0.65).

Moreover, mothers of children with autism and ASD combined were also about 33% less likely to report having taken NSAIDs during periconception and pregnancy (OR, 0.67).

Asked by *Medscape Medical News* whether she thought the protective effect from NSAIDs on ASD risk might be because anti-inflammatories reduce CRP levels, Dr. Tseng noted that their preliminary results seem to support this hypothesis, but they do not currently have data to prove it.

She speculated that NSAIDs might reduce ASD risk through inhibition of cyclooxygenase-1 (COX-1) and COX-2, both of which may play a role in fetal brain development, specifically, the dendritic branching involved in developing areas of the brain responsible for cognitive function.

Other possible biological pathways include immune signaling molecules, such as cytokines and chemokines. All potential pathways through which NSAIDs may reduce ASD risk require further study, she added.

"There isn't an absolute contraindication for NSAIDs during pregnancy," Dr. Tseng said.

"However, their effects are not fully understood, so NSAIDs are not generally recommended during pregnancy. There are potential adverse effects to both the mother and fetus as well, particularly after 32 weeks [of gestation], so the decision to take NSAIDs should be determined by the doctor and the patient, weighing the risk and benefits of doing so."

Public Health Message

Asked by *Medscape Medical News* to comment on this study, Paul Patterson, PhD, professor of biological sciences, California Institute of Technology, Pasadena, noted that infections — bacterial, viral, and even from parasites — increase the risk not only for ASD but for schizophrenia as well.

"Animal studies indicate that it's not the particular pathogen involved, it's the mothers' inflammatory response to infection that changes fetal brain development," he added.

Prevention of infection and subsequent inflammation is therefore very important for maternal and fetal health.

"Women don't recognize that infection is a serious risk, and they don't realize that they should make a significant effort to avoid infection when pregnant," Dr. Patterson said. For example, women need to avoid people who are sick.

They need to wash their hands often and thoroughly, especially after being in a public place. They also need to take advantage of preventive strategies, such as influenza vaccination, in order to minimize their risk of getting the flu.

And they should avoid eating red meat, which can contain the *Toxoplasma* parasite.

"I wrote a book about this to get people to be aware of these issues," Dr. Patterson said. "But they still aren't, so I think it's an issue of publicity."

Dr. Patterson's book is entitled *Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia, and Depression* (MIT Press).

Neither Dr. Brown, Dr. Tseng, nor Dr. Patterson have disclosed any relevant financial relationships.

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Rosalyn Baker, LMSW, LMFT, MAC