Immune system 'overdrive' in pregnant women puts male child at risk for brain disorders

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Johns Hopkins researchers report that fetal mice—especially males—show signs of brain damage that lasts into their adulthood when they are exposed in the womb to a maternal immune system kicked into high gear by a serious infection or other malady. The findings suggest that some neurologic diseases in humans could be similarly rooted in prenatal exposure to inflammatory immune responses.

In a report on the research published online last week in the journal *Brain, Behavior and Immunity*, the investigators say that the part of the brain responsible for memory and spatial navigation (the hippocampus) was smaller over the long term in the male offspring exposed to the overactive immune system in the womb. The males also had fewer nerve cells in their brains and their brains contained a type of immune cell that shouldn't be present there.

"Our research suggests that in mice, males may be more vulnerable to the effects of maternal inflammation than females, and the impact may be life long," says study leader Irina Burd, M.D., Ph.D., an assistant professor of gynecology/obstetrics and neurology at the Johns Hopkins University School of Medicine and director of the Integrated Research Center for Fetal Medicine. "Now we wonder if this could explain why more males have diseases such as autism and schizophrenia, which appear to have neurobiological causes."

For the study, researchers sought to mimic the effects of a maternal infection or other condition that causes inflammation in a pregnant mother. This type of inflammation between 18 and 32 weeks of gestation in humans has been linked to preterm birth as well as an imbalance of immune cells in the brain of the offspring and even death of nerve cells in the brains of those children. Burd and her colleagues used a mouse model to study what happens to the brains of those offspring as they age into adulthood to see if the effects persisted.

One group of pregnant mice got saline injections into the womb, while another group got injections of lipopolysaccharide (LPS), a toxin meant to generate the kind of inflammatory effects of E. coli bacteria without the presence of the germ itself.

Soon after birth, the LPS group showed poor motor skills and behavioral issues such as hyperactivity. At 60 days post-weaning—the equivalent of mouse adulthood—the LPS mice could walk well, but were still hyperactive, suggesting the motor problems had resolved, possibly through some type of rewiring of the brain, but the behavioral problems had not.

"All this time later, something was still going on in their brains," Burd says.

The sex-specific differences—the smaller hippocampus, the presence of fewer nerve cells, the existence of immune system macrophages in places they shouldn't be—were also found in adulthood.

Chronic inflammation, Burd says, may play a role in keeping the hippocampus small, potentially because it inhibits proper brain development. But why males and females respond differently to the same insult in utero remains a question.

Unraveling the sex-based mechanisms underlying the response to maternal inflammation could provide critical knowledge necessary to develop interventions and potentially new drug therapies, she says.

Provided by Johns Hopkins University School of Medicine