SCIENCE BRIEF

Neutralizing Threats to Brain Chemistry Caused by Maternal Infections

A review of a recent study that identified the immune protein, released in mothers infected with influenza, that is responsible for disrupting fetal brain development.

Each Science Brief summarizes the findings and implications of a recent study in basic science or clinical research. Studies are selected for review based on their scientific merit and contributions to understanding early development. No single study is definitive, of course. Understanding of early development is based on many studies that, taken together, permit broad conclusions and human applications. Generalizing to human children the results of studies with animals, for example, must be done cautiously and confirmed by research with children and their families. The National Scientific Council rests its work on a rigorous discussion of the validity of many studies like these conducted over many years and using different methodologies and samples. For more information, go to www.developingchild.net

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Why was the study done?

Birth in the winter and spring has long been recognized as increasing risk for certain types of psychiatric disorders, such as schizophrenia, but little has been known about how this occurs and what might be done to mitigate the risks. Influenza epidemics particularly have been related to the increased prevalence of diagnosed psychiatric disorders, determined through examination of medical records of thousands of women in the United States and other countries. Maternal infection during pregnancy is generally recognized as a risk factor to the offspring for cognition deficits and other developmental disabilities. Disturbances in the early prenatal environment can result in disturbed development of brain architecture, which leads to long-term consequences for the lifetime of the individual. But *how* does maternal infection impact the development of brain architecture and chemistry? Some scientists have suggested that infections that reach the fetus are the major cause of the subsequent health problems. Others, including the authors of this study, have proposed that the infection stimulates an immune response by the pregnant mother, known as maternal immune activation (MIA), which results in the production of naturally occurring immune substances. These substances are important for fighting infections, but they can have detrimental effects on the brain development of the fetus. In past research, the authors have utilized a powerful animal model that was able to demonstrate that the immune response of the pregnant mother was responsible for causing long-term changes in brain architecture and behavior. How this occurred was a mystery. The authors here had a goal of identifying the immune substances that may be responsible for disrupting brain development, and to determine if interfering with these immune substances could be a powerful intervention for preventing disturbances in brain architecture, chemistry, and behavior.

What did the study find?

When the authors injected pregnant mice with an immune substance that they suspected might be the cause for disrupting brain development, a protein known as interleukin-6 (IL-6), they observed

profound long-term effects on the offspring. This treatment does not cause a typical MIA directly, but it does mimic the increase in IL-6 production that occurs during an MIA in pregnant mice. Remarkably, a single injection of IL-6, at a time corresponding to the first trimester of human fetal development, resulted in the offspring exhibiting long-term deficits in controlling their emotional state, in their normal exploratory behavior and in their willingness to socially interact with other mice. The authors injected one other major immune substance, interferon, and found no such deficits, suggesting that IL-6 was a key immune protein. To prove this definitively, the authors did two additional experiments. First, the authors used their model of causing a general immune response in pregnant mice, but this time co-administering an antibody to IL-6 that helps eliminate IL-6 from the maternal blood stream. This treatment completely prevented the behavioral deficits from ever occurring. Second, the authors tried their maternal infection model in mice that had the gene encoding IL-6 deleted permanently—the mothers do not produce IL-6 during an infection, instead using other immune chemicals to wage an immune battle. Here, the offspring also did not exhibit the behavioral disturbances. Finally, in these studies, the authors showed that administration of IL-6 caused certain changes in brain chemistry of the offspring that correlated with the deficits in behavior. They showed that the preventive measure of administering antibodies to IL-6 to pregnant mice at the same time as injecting IL-6 completely prevented the chemical changes in the brain of the offspring.

How was the study conducted?

Several different experimental groups of pregnant mice were used. Mice have a 20-day gestation period, and these were injected on embryonic day 12, corresponding to the first trimester of human fetal development. The fetal brain is just beginning to take shape in terms of its emerging architecture, with many brain cells being produced and the initial phase underway of making connections between cells. One set of pregnant mice was administered a single injection of IL-6, or a combination of IL-6 and an antibody that neutralizes IL-6. A second set of mice was injected with another immune chemical, interferon, which also is produced by pregnant mice as part of MIA. A third set of mice that had a deletion of the gene encoding IL-6 was injected with a chemical mixture, including influenza virus proteins that stimulate a maternal immune response. In all instances, the offspring were born, showed normal nursing skills and weight gain through the time that they are weaned (postnatal day 21) and were tested behaviorally on a number of tasks as young adults. The tests examined the degree to which the mice were able to be distracted (a measure of attention), their eagerness to explore their environment, and their willingness to interact socially with other mice. The brain tissue from some of the mice also was examined subsequently for changes in brain chemistry, determined using a complex method that can measure the expression of thousands of brain genes at one time. The information was analyzed to determine if the normal patterns of gene expression are changed in the offspring in which the pregnant mother was injected with IL-6, or in offspring in which IL-6 was neutralized.

What do the findings mean?

The results have implications for understanding how maternal health can directly impact fetal brain development, with long-term implications for brain architecture, chemistry, and function. The authors not only were able to identify the specific immune substance that is responsible for disrupting fetal development, but they also proved that neutralizing the substance is an effective preventative treatment. The finding will allow scientists to determine how IL-6 specifically interferes with fetal brain development and which aspects of emerging brain architecture are most vulnerable. Eventually, research in animal models can be done to see if administering the neutralizing agent *after* onset of maternal infection can be as effective in preventing disturbances in fetal development as the paradigm used here, in which the antibody to IL-6 was given at the same time. These findings have significant implications for developing more aggressive prevention and treatment strategies for women who

contract influenza and other infections when pregnant, in order to avoid long-lasting disruptions in the brain chemistry of their babies.

Study Title and Authors

Smith, S.E.P., Li, J., Garbett, K., Mirnics, K. & Patterson, P.H. (2007). Maternal immune activation alters fetal brain development through interleukin-6. *Journal of Neuroscience*, 27:10695-10702.