A Theory That Raises Questions
Schizophrenia Risk May Start in Womb

By Shankar Vedantam
Washington Post Staff Writer
Tuesday, November 27, 2007; HE01

Over the past several decades, a steady stream of studies has documented that people born in winter and spring have an increased risk for schizophrenia, a serious mental illness characterized by disordered thinking, hallucinations and other psychotic symptoms.

Explanations for the increased risk have ranged from the astrological -- different signs of the zodiac have been associated with various mental problems -- to accounts that suggested the risk came from seasonal variations in sunlight.

In recent months and years, scientists have developed a different explanation: Studies show the increased risk of schizophrenia appears linked to maternal infections during the first and second trimesters of pregnancy -- especially flu infections. Since the flu peaks in the fall, this might explain why babies born in the winter and spring have the higher risk.

The research is both intriguing and troubling. For one thing, it suggests that the origins of diseases such as schizophrenia might start as early as the womb. Indeed, symptoms of schizophrenia, which typically emerge in late adolescence or early adulthood and affects about 1 percent of the population, may only be the very last stage in a long process.

"Often what we see in the form of schizophrenia, bipolar disorder and even some of the more neurological disorders like Alzheimer's disease [is] the end stage where people show symptoms," said Thomas Insel, director of the National Institute of Mental Health. "The best model is in Parkinson's disease: You don't show the symptoms until you have lost 80 percent of the neurons in the substantia nigra," an area of the brain that helps produce the neurotransmitter dopamine.

But if research into the links between early maternal infections and schizophrenia might one day provide researchers with clues about how to attack the disease before symptoms become apparent, it also raises difficult public health conundrums.

That's because the newest studies suggest the culprit may not be infections such as the flu per se, but pregnant mothers' immune reactions to such infections. Current guidelines recommend that pregnant women get a flu shot -- and the point of the flu vaccine is to set off an immune reaction. If the risk for schizophrenia is increased as a result of maternal antibodies, might protecting mom and baby from the flu raise the risk the child could get schizophrenia years down the road?

The research into the links between maternal flu and schizophrenia is still considered preliminary, which makes any policy conclusions premature, but scientists studying the connection are starting to worry.
National guidelines issued by the [Centers for Disease Control and Prevention](http://www.cdc.gov) recommend that pregnant women get flu shots.

"Obviously, the safe thing to do is to go with the experts, and the experts are the CDC," said Paul Patterson, a professor of biology at the [California Institute of Technology](http://www.caltech.edu) and one of the leading researchers into the link between maternal infections and schizophrenia. "However, if it was my wife, I would not [want] her vaccinated."

Patterson said he would try to protect a pregnant family member from the flu by suggesting she keep away from infected people and by enforcing a regimen of regular hand-washing among all family members.

However, he conceded that such measures might not be as effective as flu shots and that women who get the flu because they don't get a flu shot might not only put their future children at increased risk for schizophrenia, but also incur numerous other risks from the illness. Careful prevention techniques, moreover, are unlikely to help pregnant women who have toddlers, because small children tend to bring home endless streams of viral infections.

Insel praised Patterson's research into the connection between infections and schizophrenia, but he warned against rushing to revise flu shot recommendations.

"It raises a question but does not provide an answer," Insel said of the newest research. "We are not ready to jump from any of this to the policy dimension."

**The Evidence**

Hints about the schizophrenia-winter connection have been around for decades.

Epidemiologists have found that children of women who were pregnant during widespread flu epidemics seemed to have higher risk for schizophrenia. But critics have said there's insufficient evidence to assert a causative relationship because such studies did not confirm that the pregnant women had the flu.

Besides, other factors seemed to trigger the same effect: One wartime study found that pregnant women whose husbands died were more likely to have children who later developed schizophrenia.

A research breakthrough came in 2004 when Alan Brown, a psychiatrist at [Columbia University](http://www.columbia.edu) and the New York State Psychiatric Institute, got access to data from a study that collected blood samples between 1959 and 1966 from thousands of pregnant women at different stages of their pregnancy.

In an analysis that compared blood samples from the mothers of 64 children who went on to develop schizophrenia with blood samples of similar mothers whose offspring did not, Brown and his colleagues showed that women who had higher levels of influenza antibodies in their first or second trimester of pregnancy had offspring who were three to seven times more likely to develop schizophrenia.

Brown calculated that if the women had not had the flu during pregnancy, 14 percent of the schizophrenia cases could have been prevented, an effect he calls potentially enormous for a disease believed to have several complex genetic and environmental factors.

Brown and other researchers also began seeking evidence that mothers who contracted other infections during pregnancy also had children who were at increased risk of schizophrenia; they also began looking for
common pathways between the infections. One appeared to be an immune system protein, or cytokine, called interleukin-6; cytokines are activated not only through infections but also through stress.

Brown, Insel and Patterson all hasten to point out that, while schizophrenia is a relatively rare disease, as many as 10 percent of women get the flu while they are pregnant, and many pregnant women contract other infections and experience stress. This suggests that the vast majority of women who have their immune systems triggered during pregnancy will not have children who develop schizophrenia.

Insel also cites evidence that genetics may play a more dominant role than the environment in determining who gets schizophrenia: Studies of identical twins show that when one child develops schizophrenia, the other has a 50 percent chance of developing the disorder, too.

However, some of the increased risk among identical twins may be a result of maternal infections during pregnancy -- and not genetics, Patterson argues. That's because those identical twins who share a common placenta -- and who are, therefore, more likely to receive the same maternal cytokines -- seem to have a higher risk of schizophrenia than identical twins who do not share a common placenta.

(While the science assigns no blame to mothers for these risks, the long history of blaming parents for the disorder suggests it might be useful to note that people's immune systems are beyond their control, and pregnant women cannot be held responsible for the flu-schizophrenia link.)

E. Fuller Torrey, a Washington psychiatrist with a long interest in schizophrenia, said the link between early maternal infections and schizophrenia is strong. He believes that infections and immune reactions in young children, not just maternal infections during fetal life, might be involved in elevating the risk for schizophrenia.

Animal research conducted by Caltech's Patterson along with William Carpenter and James Koenig at the Maryland Psychiatric Research Center at the University of Maryland appears to support the theories of Brown and others.

Pregnant rodents given flu infections seem more likely to have offspring that show some of the behavioral symptoms of schizophrenia, such as social withdrawal and anxiety. When the effect of maternal antibodies is blocked, the offspring do not go on to develop such symptoms.

Patterson said he also hoped to see new epidemiological studies that specifically looked at whether pregnant women given flu shots had offspring with a higher risk of schizophrenia than pregnant women who did not receive flu shots.

"It is true that vaccinations do not cause the same degree of immune activation as an infection," he said. "But if you are recommending universal vaccinations for every woman who is pregnant, you are asking for increased risk for schizophrenia because some women are going to have a very strong reaction."

What should pregnant women do until useful policy conclusions can be drawn?

Experts say the best bet is probably to stick to official public health guidelines on the flu shot, and to try to limit infections and stress during pregnancy.

"I was raised in the Midwest, so I believe the best motto is, 'Everything in moderation,' " Koenig said.
"Keep your life as well balanced as possible." 

Comments: vedantams@washpost.com.

Post a Comment

View all comments that have been posted about this article.

You must be logged in to leave a comment. Log in | Register

Comments that include profanity or personal attacks or other inappropriate comments or material will be removed from the site. Additionally, entries that are unsigned or contain "signatures" by someone other than the actual author will be removed. Finally, we will take steps to block users who violate any of our posting standards, terms of use or privacy policies or any other policies governing this site. Please review the full rules governing commentaries and discussions. You are fully responsible for the content that you post.

© 2007 The Washington Post Company

Ads by Google

Neulasta® (pegfilgrastim)
Be proactive. Protect yourself right from the start of chemo.
www.Neuasta.com