Maternal infection during pregnancy and schizophrenia

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For the 2007–2008 season, the Canadian National Advisory Committee on Immunization has for the first time recommended that all pregnant women be vaccinated against influenza. In the United States, the Centers for Disease Control and Prevention have recommended influenza vaccination for pregnant women in the second and third trimester of pregnancy since 1997; in 2004, this recommendation was revised to include pregnant women in all trimesters (see Mak and colleagues[1] for further discussion of current policies on influenza vaccination during pregnancy in other countries). Although the decision to vaccinate is based mainly on the increased risk in pregnant women for acute cardiopulmonary complications due to influenza, increased influenza vaccination during pregnancy could have implications for the development of schizophrenia.

For a few decades now, maternal infection during pregnancy has been considered a plausible risk factor for schizophrenia. The story essentially began in Finland with the publication in 1988 of a paper by Mednick and colleagues[2] reporting an increased risk for schizophrenia in people who were fetuses during the 1957 influenza epidemic. The story has continued up to the publication in December 2007 of a study coming again from Scandinavia, this time from Denmark. Using a much more sophisticated database (i.e., a national longitudinal registry of health records), this study again showed an increased risk for schizophrenia associated with maternal influenza during pregnancy.[3] During the intervening 20 years, more than 25 epidemiologic studies have examined this issue, using various sources for information on the infection, ranging from simple correlation with known dates of epidemics to maternal recall, hospital records and national registry records on documented influenza occurrence. About one-half have replicated the finding, and about one-half have not. These failures to replicate could be due to inaccurate information on infection or other factors, or they may represent true findings of no association between maternal influenza and schizophrenia in some populations. Interestingly, increased rates of diagnosis for major affective disorder have also been reported following exposure to an influenza epidemic during the second trimester,[4] indicating that effects may not be specific for schizophrenia.

In addition to influenza, a wide variety of other maternal infections during pregnancy have been reported to be associated with increased risk for schizophrenia. These include maternal infections with other viruses (measles, rubella, varicella-zoster, polio) as well as maternal bronchopneumonia (which is largely bacterial), maternal infection with the parasite causing toxoplasmosis and infections of the maternal genital and reproductive systems. The rubella study is particularly striking in that up to 20% of subjects exposed to rubella (serologically confirmed) in the first trimester developed adult schizophrenia.[5] Thus it appears that maternal infection with a wide variety of agents might potentially increase risk for schizophrenia, suggesting that factors common to many infections may be mechanistically responsible.

More recently, some laboratories have attempted to confirm maternal infection more precisely by analyzing antibodies for viral infection in maternal serum that had been stored from 30 to 40 years until offspring had grown and developed schizophrenia. As can be appreciated, these are very challenging studies with limits in the sample size due to limited availability of stored serum, questions about storage and stability of samples, etc. Studies by Brown and colleagues[6] found an association between schizophrenia spectrum disorders and maternal influenza during the first trimester of pregnancy that just missed statistical significance ($p = 0.08$) and during the first half of pregnancy that also barely missed significance ($p = 0.052$). Interestingly, while earlier epidemiologic studies had quite consistently implicated influenza in the second trimester of pregnancy, Brown and colleagues' studies with archived maternal serum have implicated the first third to half of pregnancy. It has been pointed out that, if the association between maternal influenza and schizophrenia holds, then maternal influenza could account for an

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appreciable amount of the population-associable risk for schizophrenia because influenza is so prevalent. Clearly, these important studies require replication and confirmation.

Other studies examining serologically confirmed maternal infection are those published by Buka and colleagues from the US National Collaborative Perinatal Project.[7] Assaying maternal serum taken at the end of pregnancy, these studies have reported that elevated titres of maternal antibodies to herpes simplex virus type 2 (HSV-2) are associated with increased incidence of psychosis (both schizophrenic and affective combined, and schizophrenic alone) in offspring. It was noted that the effect sizes for these associations were comparable in magnitude to those reported for some genetic polymorphisms linked to schizophrenia. However, by contrast, Brown and colleagues found no significant association between seropositivity for HSV-2 in late pregnancy maternal serum and risk for schizophrenia spectrum disorders in offspring in their sample population.[8]

Overall, it is noteworthy that, with the exception of studies of influenza, most of the epidemiologic studies implicating prenatal infection with various agents as risk factors for schizophrenia have been reported only by single groups and await replication by others. As an interesting twist, controlling for a series of confounders, Sørensen and colleagues[9] have reported that maternal exposure to analgesics (ASA and other anti-inflammatory agents, codeine and, rarely, morphine) in the second trimester of pregnancy is also associated with an increased risk for schizophrenia. If maternal infection is a risk factor for schizophrenia, it is also evident that the epidemiologic studies have not yet clearly defined which stage of pregnancy might be the main vulnerability period. Both the first and second trimesters have been implicated.

Of course, maternal infection during pregnancy is not thought to be the sole cause of schizophrenia but is speculated to act in interaction with other etiologic factors. For example, the effects of prenatal infection on fetal neurodevelopment may be exaggerated in those with a particular genetic vulnerability. As another example, patients with schizophrenia who were exposed to second trimester influenza have been reported to be more likely to have experienced a subsequent obstetric complication and to have had a lower birth weight, compared with patients who did not have second trimester exposure.[10]

Since 2000, there has been a veritable explosion of animal studies designed to ask whether it is plausible that maternal infection during pregnancy could cause changes in brain development relevant to schizophrenia. These studies have modelled maternal infection either using live influenza viruses or using viral RNA mimics or bacterial endotoxin to produce more controlled infections. Overall, a large number of studies have now demonstrated that, in rodents, maternal infection during pregnancy can indeed produce changes in central nervous system (CNS) structure, function and behaviour in offspring. These changes include many relevant to schizophrenia, such as deficits in prepulse inhibition of startle, latent inhibition, memory and social interaction; increases in amphetamine- and MK-801–induced locomotion; alterations in CNS levels of dopamine and tyrosine hydroxylase; and cell death, cell atrophy or reduced volume in the hippocampus. Although the overall conclusion from these studies supports the idea that maternal infection can alter brain development, as in many fields, each laboratory works with its own particular model, precluding across-laboratory replication of specific findings. Thus each laboratory works with its own species (rat, mouse), dose and type of infectious agent (virus, viral mimic, bacterial endotoxin) given at different times of gestation, and each laboratory tends to measure different end points in offspring.

Work in the area of animal modelling is now also attempting to approach the question of the mechanism by which a maternal infection might affect fetal brain development. Several possibilities are being considered:

1. Live virus may directly reach and affect the fetal brain. This has been supported by one study employing intranasal administration of influenza virus to pregnant mice,[11] although not by another.[12]
2. Chemical mediators of infection may mediate changes in brain development. During a maternal infection, chemical mediators of inflammation, most prominently the cytokines, interleukin-1β (IL-1β), IL-6 and tumour necrosis factor-α, are increased in the mother's blood and in the placenta. It is still unclear whether these are routinely increased in the fetal brain after maternal infection. Such cytokines could affect fetal brain development by direct effects on fetal brain, by compromising placental function or by effects mediated through the mother.
3. Fever itself, as a consequence of increased maternal cytokine release, may affect fetal neurodevelopment. Research in the field of exercise physiology undertaken owing to concerns about increases in maternal body temperature during exercise in pregnancy have shown that quite brief exposure of pregnant rodents to temperatures from 40°C to 43°C can result in fetal resorption and CNS anomalies. For example, Khan and Brown[13] have shown that maintaining pregnant rats at 42°C for 45 minutes on gestation day 17 is sufficient to increase apoptosis in the cerebral cortex of fetuses. (One wonders about such effects in the face of global warming and record summer temperatures in several countries.)
4. It has been suggested that antibodies against infectious agents may cross react with and injure fetal brain structures. There is not yet evidence that such an autoimmune mechanism occurs in schizophrenia. However the notion is not without precedent. For example, there is some experimental support for the idea that antibodies against Group A β-hemolytic streptococci may cross-react with basal ganglia, leading to cases of Tourette syndrome or obsessive–compulsive disorder following strep throat infections.[14]
5. Medications such as analgesics and anti-inflammatory drugs taken during an infection in pregnancy could affect fetal development.

If maternal infection is a clear risk factor for schizophrenia, this raises several clinical questions for prevention. Should maternal influenza vaccination be more aggressively promoted? What about prevention of other infections? Do

anti-inflamatory/antipyretic drugs have positive or negative effects? Is reduction of fever sufficient, or should inhibition of specific cytokines be targeted? Etc.

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