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Womb flu link to schizophrenia

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ABSTRACT Schizophrenia is a distressing and disabling condition, affecting about 1% of the population worldwide. It is caused by an interaction of genetic and environmental factors which can have their effect *in utero* and throughout development. Investigation of *in utero* risk factors for schizophrenia is fraught with methodological difficulties. Recent news reports highlighted work, by Columbia University, which overcomes some of these problems. Dr Brown and colleagues have shown, in line with previous investigations, that maternal influenza infection leads to a modest increase in the risk of developing schizophrenia. The mechanism of this action is unknown, but it is probably indirect. It is too early to make public health policy recommendations regarding flu vaccination.

KEYWORDS Influenza, maternal exposure, risk factors, schizophrenia

LIST OF ABBREVIATIONS Relative risk (RR)

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Schizophrenia is a mental disorder with a very variable presentation, characterised by delusions, hallucinations and an insidious deterioration in cognitive and social functioning. It is one of the 30 leading causes of disability and mortality worldwide and affects about 1% of the UK population at some time in their lives, with an average age of onset in the mid-twenties.[1]

BACKGROUND

Our understanding of the cause of schizophrenia is incomplete but it is certain that individual genetic make-up is very important, and in addition that the genetic make-up interacts with environmental factors to produce the disease. While genetic make-up is fixed at conception, environmental influences vary throughout the life of the individual; those that have been implicated, at one time or another, in the development of schizophrenia are numerous and diverse and their mechanisms of action are obscure. However, there is evidence that the following factors play a part in some people: being an immigrant or from an ethnic minority; maternal infection, famine or bereavement during pregnancy; being born in winter or spring; obstetric complications; being born and brought up in an urban area; and using illicit substances as a teenager.

WOMB FLU LINK

News reports, prompted by a recent paper by Dr Alan Brown[5] and colleagues at Columbia University, have highlighted the relationship between maternal influenza infection and an increased risk of developing schizophrenia or a related disorder.

FLU RESEARCH

Sixteen years ago, Mednick and colleagues[6] first reported an increased risk of schizophrenia in a study of Finnish individuals whose mothers had been in the mid-part of their pregnancy during the worldwide influenza epidemic of 1957. While this provided indirect evidence that influenza might be implicated in the causation of schizophrenia, of the 26 further investigations that tried to replicate this finding, about half found no association. None of these studies was able to give a definitive answer, mainly because, like the Mednick study, they defined *in utero* 'exposure' to influenza on the basis of indirect evidence, such as dates of flu epidemics or the recollections of mothers whose children had gone on to develop schizophrenia.

NEW EVIDENCE

In an attempt to avoid some of these methodological problems, Brown and colleagues examined archived maternal serum specimens, collected prospectively throughout pregnancy, in a group of mothers who took part in the Child Health and Development Study in California, USA from 1959 to 1966. The samples were tested for antibodies to determine if the mothers had flu during pregnancy. In addition, their adult offspring were followed up by screening computerised inpatient, outpatient and pharmacy registries; this detected 183 offspring with possible psychotic illness. These individuals were then either interviewed by research psychiatrists in a standardised fashion or had diagnoses made by careful examination of their notes. In total, 64 patients had schizophrenia or schizoaffective disorder (a closely

related condition). When these patients were compared with 125 carefully matched controls, Brown and colleagues found that exposure to influenza in the first half of pregnancy was associated with a three-fold increase in RR of schizophrenia or schizoaffective disorder. How does this compare with previous work and other risk factors?

SIZE OF EFFECT

A three-fold increase in relative risk after maternal influenza exposure is similar to that found in other studies but is modest when compared with, for example, that of other environmental risk factors such as prenatal rubella (RR ~5) or perinatal brain damage (RR ~7). It is relatively small when compared to genetic risk factors such as, for example, having an affected parent (RR ~10) or an affected twin (RR ~50).

INDIRECT ACTION

Animal models of influenza infection suggest that the virus can have a direct effect on the developing brain, but it is believed that the virus rarely crosses the placenta in humans. Accordingly, its effects on the fetal brain are likely to be indirectly mediated. Certainly, molecules produced by the mother in response to infection, such as antibodies and cytokines, can cross the placenta and, theoretically, may interfere with brain development. Other proposed mediators include maternal hyperthermia and over the counter, aspirin-containing flu remedies (these are not usually recommended at any stage of pregnancy).

IN CONTEXT

Overall, this new research adds persuasive evidence to the argument that there is a connection between maternal infection during pregnancy and development of schizophrenia many years later. Although the mechanism of action is unknown, it seems likely that maternal flu increases relative risk of developing schizophrenia by about three; this means that an individual with no family history of schizophrenia would have their lifetime risk increased from about 1% to about 3%. It is perhaps pertinent to ask, how should this information affect our behaviour?

FLU VACCINATION

The present study provides further evidence that flu infection during pregnancy is a risk factor for schizophrenia. However, it is based on relatively small numbers of patients and cannot be regarded as conclusive. Flu vaccination can prevent influenza infection during pregnancy and, as such, has the potential to reduce the risk of a child developing schizophrenia in later life. On the other hand, it is possible that innoculating healthy women during pregnancy could lead to adverse consequences in later years. The American Centre for Disease Control is recommending that, as there is a shortage of flu vaccinations at present, women who will be pregnant this flu season should have priority. Despite this, as the authors of the Columbia University study recently stated, it would seem prudent to 'caution against making any public health policy recommendations until these links have been confirmed.'

KEYPOINTS

- Schizophrenia is a distressing and disabling condition, affecting about 1% of the population worldwide.
- It is caused by an interaction of genetic and environmental factors which can have their effect *in utero* and throughout development.
- Maternal infections, including influenza, can modestly increase the risk of developing schizophrenia.
- Recent evidence, in line with previous work, supports this assertion.
- The mechanism of this action is unknown, but it is probably indirect.
- It is too early to make public health policy recommendations regarding flu vaccination.

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