



Prenatal Exposure to Influenza and the Risk of Subsequent Development of Schizophrenia

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Abstract

Various events occurring during pregnancy might influence the normal neurogenesis of fetus brain, including exposure to the influenza virus. Several studies have attempted to find a relationship between exposure to influenza virus and the onset of schizophrenic behavior in childhood or adulthood, however results remain contradictory. In this review we describe several animal and human studies that show or do not show a relationship between exposure to the influenza virus during pregnancy and the subsequent development of schizophrenia.

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After about 100 years of modern research the causes of schizophrenia remain an open question. It has been postulated that various events occurring during pregnancy might influence normal neurogenesis. Several obstetric complications – mainly diabetes, Rhesus incompatibility, bleeding, preeclampsia, premature rupture of membranes and preterm birth – may double the risk of schizophrenia in exposed offspring [1]. Recently, several studies in the northern hemisphere [2–4] have suggested a link with exposure to the influenza virus. The most widely studied and frequent seasonal factor suspected, which may increase the risk of subsequent development of schizophrenia, is influenza infection during the second trimester of pregnancy [5]. Similar associations have been made for rubella, measles, varicella zoster, and diphtheria [3,6]. It is possible that maternal viral infection influences fetal brain development through the response of the mother's immune system. It is therefore postulated that exposure to infection during fetal life disrupts key events in the formation of critical brain structures and causes neurophysiologic alternations, which increase the vulnerability to schizophrenia in adulthood. Several studies aimed at finding a relationship between exposure to influenza virus and the onset of schizophrenic behavior in childhood or adulthood have been conducted, but results remain contradictory.

Evidence of association between prenatal influenza and schizophrenia

Several studies have attempted to find a relationship between exposure to influenza virus and the onset of schizophrenia in adults [Table 1]. Watson et al. [3] found that schizophrenic birth seasonality correlated with winter but not summer diseases, and birth seasonality did not vary with winter or summer temperature extremes. Among winter diseases, diphtheria, pneumonia and influenza appeared to be more involved in the subsequent development of schizophrenia. The effect appeared among unmarried but not married schizophrenic patients. From this it was suggested that the relationship is specific to a more severe deterioration of disease. In the context of a Finnish birth cohort, Mednick et al. [5] reported that influenza viral infection during the latter two-thirds of fetal development increased the risk of adult schizophrenic outcome. Barr and co-workers [7] replicated earlier findings of an association between exposure to influenza in the second trimester of gestation and adult schizophrenia. However, although the relatively simple statistical method they used made allowance for the spring excess of schizophrenic birth, it made no allowance for the rising number of schizophrenics in their patient population in successive decades. O'Callaghan et al. [8] reviewed control years (2 previous and 2 subsequent years) and noted that 5 months after the peak infection prevalence, the number of births of individuals who later developed schizophrenia was 88% higher than the average number of such births in the corresponding periods of the 2 previous and the 2 subsequent years. However, there was no direct evidence that the mothers of the individuals who developed schizophrenia were infected with the virus.

One of the largest studies was conducted by Adams et al. [9], who explored the relationship between the monthly incidence of influenza (and measles) in the general population and the distribution of birth dates in three large series of schizophrenia patients in Scotland, England and Denmark. Exposure to the 1957 epidemic of A2 influenza in mid-pregnancy was associated with an increased incidence of schizophrenia, at least in females, in all three countries. Takei and colleagues [10] investigated a sample also from Denmark and noted that exposure to influenza 4 months prior to birth (i.e., about the 6th month of gestation) was significantly associated with an increased risk of later schizophre-

Table 1. Studies showing the relationship between exposure to influenza virus in mid-pregnancy and the consequent development of schizophrenia in adults

First author, year	Country	No. of samples	Relationship	Trimester	Comments
Watson, 1984	USA	3,246	+ + +	2nd	Influenza virus, diphtheria and pneumonia appeared to relate to the development of schizophrenia
Mednick, 1988	Finland	1,781	+ + +	2nd	
Kendell, 1989	Scotland	18,476	-		
Barr, 1990	Denmark	7,239	+ + +	2nd	
O'Callaghan, 1991	England	339	+ + +	2nd	
Crow, 1992	England	15,098	-		
Adams, 1993	Scotland, England, Denmark	16,960 22,021 18,723	+ + +	2nd	The relationship was found mostly in female schizophrenic patients
McGrath, 1994	Australia		+ +		
Selten, 1994	Dutch database	4,634	-		
Susser, 1994	Holland	1,371	-		
Kunigi, 1995	Japan	1,284	+ +	2nd	The relationship was found mostly in female schizophrenic patients
Takei, 1996	Denmark	9,462	+ + +	2nd	
Isumoto, 1996	Japan	941	+ + +	2nd	The relationship was found mostly in female schizophrenic patients
Cannon, 1996	Ireland	570	-		
Morgan, 1997	Australia	1,852	-		A possible effect of influenza on subsequent development of mental retardation
Selten, 1999	Netherlands	1,116	-		Patients with first hospitalization in a psychiatric hospital
Mino, 2000	Japan		-		
Limosin, 2002	France	974	+ +	2nd	
Brown, 2004	USA	189	+ + +	1st	Maternal sera that were assayed for influenza antibodies

nia. The number of schizophrenic births was found to have risen by 12% (95% confidence interval 1–24%) for every 100,000 cases of influenza in the 4th month before birth.

McGrath et al. [11], following their analysis of the 1954, 1957 and 1959 epidemics of A2 influenza, proposed that infants born between 4 and 6 months after an influenza epidemic onset have an increased risk of schizophrenia. Four months after the onset of the 1954 epidemic there was a significant excess of male schizophrenia births. In 1957, there was a significant excess of female schizophrenia births in the 5th month after the onset of the epidemic. The 1959 epidemic was not associated with any significant excess of male or female schizophrenic births.

Similar studies in Japan by Kunugi [12] and Izumoto [13] and their teams yielded similar results that replicate their earlier findings – namely, that schizophrenic births increased mostly among females who were exposed to influenza epidemics in the 5th month of gestation. This pattern was not observed in male subjects. The limitation of Izumoto's study was that it included patients from many different facilities and lacked a test for the reliability of diagnosis.

More recently, in a study in France, Limosin et al. [14] examined 974 adults with schizophrenia who were compared for risk of exposure to influenza with their non-schizophrenic siblings and with matched controls. Significantly more schizophrenic subjects than controls had been exposed to the influenza virus during the 5th month of pregnancy.

In order to more definitively test this hypothesis, Brown and associates [15] conducted assays for influenza antibody in serum samples drawn from pregnant women whose offspring developed schizophrenia, and compared these assays with a matched comparison group. They examined a 64 birth cohort diagnosed as having schizophrenia spectrum disorders (mostly schizophrenia and schizoaffective disorder). The controls were 125 members of the birth cohort who had not been diagnosed as having a schizophrenia spectrum or major affective disorder. The risk of schizophrenia was increased sevenfold for influenza exposure during the first trimester. The pattern was not found for the second or third trimester. With the use of a broader gestational period of influenza exposure – early to mid-pregnancy – the risk of schizophrenia was increased threefold. However, these findings did not

achieve statistical significance and the study was based on a small sample.

Almost all the studies presented here have several limitations: a) There was no direct evidence that the subjects actually suffered a viral infection, or how many other individuals were infected subclinically and thus did not seek medical attention. b) The findings were based on hospital diagnoses of schizophrenia and influenza, rather than on strict research diagnostic standards. c) The timing of gestation was based on birth date and the authors did not know which of the subjects in the sample were born prematurely.

Studies showing absence of correlation

In contrast, several studies have shown no correlation between prenatal exposure to influenza and subsequent development of schizophrenia. Based on the admission statistics of Scottish psychiatric hospitals, Kendell and Kemp [16] looked at two different data sets. They did not find any increased risk associated with the 1918–1919 or 1957 epidemics of A2 influenza and the development of schizophrenia in Scotland. However, an association was observed

in Edinburgh. Their analysis was based on numbers of births per month rather than birth rates relative to the general population, and their controls were the 2 previous years rather than a combination of earlier and later years.

Selten and Slaets [17], in two studies, examined not only schizophrenic inpatients but also whether second-trimester exposure to the 1957 A2 influenza epidemic was associated with an increased risk of paranoid states or other non-organic psychoses in the Dutch population. They found no relationship. Similar studies were conducted by Susser et al. [18] in Holland and by Erlenmeyer-Kimling et al. in Croatia [19]. These researchers, respectively, compared the risk of schizophrenia in Dutch and Croatian birth cohorts that were or were not exposed during the second trimester of gestation to the 1957 A2 influenza epidemic. Exposed birth cohorts did not have a higher risk of schizophrenia. Also, in Japan, Mino et al. [20] did not observe any relationship between influenza epidemics and schizophrenic birth.

Morgan and team [21] analyzed the psychiatric case registry regarding diagnoses of schizophrenia, affective psychoses, or neurotic depression (comparison group) in Western Australia. The data were examined for effects associated with six influenza epidemics in the period 1950–1960. However, they did not find any major effect that could be identified as maternal influenza on the incidence of schizophrenia, affective psychoses and neurotic depression, despite sufficient statistical power to detect an effect. But they did find a possible effect for mental retardation in males exposed in the first- and second-gestational trimester.

Two studies examined the association of *in utero* exposure to the influenza virus and schizophrenic birth by means of a cohort study design. Crow and Done [22], in an investigation of the subsequent psychiatric admissions of people born a few months after the 1957 epidemic, found that the children of 945 mothers who actually suffered from influenza during the second trimester of pregnancy were at no greater risk of developing schizophrenia than children of mothers who were not infected. Only three of them were diagnosed as having had schizophrenia. Cannon and collaborators [23] traced a cohort of individuals known to have been exposed to the 1957 influenza epidemic during gestation and an unexposed cohort matched for the period of gestation and hospital of birth in Dublin. The relative risk for developing schizophrenia for the exposed subjects was 1.10. Four cases of schizophrenia were found: 2 from the 238 exposed cohort and 2 from the 284 unexposed. These findings are far from conclusive due to the small number of exposed cases.

The limitations of these studies are similar to those in previous studies – namely, hospital diagnoses are less reliable than diagnoses based upon direct interview, maternal influenza could not be assessed in individual mothers, and the timing of gestation was based on the month of birth.

Animal experimental model

Considering repercussions of the influenza virus on fetal neuronal development, Fatemi et al. [24] investigated the role of exposure of pregnant mice on day 9 of pregnancy to a sub-lethal intranasal administration of influenza virus. This has both short-term and

long-lasting deleterious effects on the developing brain structure in the progeny, as evident by altered pyramidal and non-pyramidal cell density values, atrophy of pyramidal cells despite normal cell proliferation rate, and final enlargement of brain. Moreover, abnormal corticogenesis is associated with development of abnormal behavior in the exposed adult mice. All of these findings are similar to those observed in schizophrenic patients.

In a further study, Fatemi and co-workers [25] hypothesized that human influenza infection in 9 day pregnant mice would alter the expression of glial fibrillary acidic protein (an important marker of gliosis, neuron migration, and reactive injury) in the developing brains of mice on postnatal days 0, 14 and 35. The GFAP-positive cells in prenatally exposed brains showed hypertrophy and more stellate morphology. These results suggest a significant role of prenatal human influenza viral infection on subsequent gliosis, which persists throughout brain development in mice from birth to adolescence.

Postmortem human brain studies also provide evidence for reduction in Reelin mRNA (an important secretory protein responsible for normal lamination of the brain) in schizophrenic patients. Fatemi and colleagues [26] observed that prenatally infected murine brains from postnatal day 0 showed significant reductions in Reelin-positive cell counts in a layer of neocortex and other cortical and hippocampal layers when compared to controls. Moreover, prenatal viral infection led to decreases in neocortical and hippocampal thickness. These results indicate a potential role of prenatal viral infection in the causation of neuronal migration abnormalities via reduction in Reelin production in neonatal brains.

As in schizophrenia and autism, offspring displayed deficits in prepulse inhibition in the acoustic startle response. Shi et al. [27] noted that respiratory infection in pregnant mice with the human influenza virus yields offspring that display highly abnormal behavioral responses as adults. Compared with control mice, the infected mice also displayed striking responses to the acute administration of antipsychotic (clozapine and chlorpromazine) and psychomimetic (ketamine) drugs. Moreover, these mice were deficient in exploratory behavior in both open-field and novel-object tests, as well as in social interaction. At least some of these behavioral changes are likely to be attributable to the maternal immune response itself. In other words, maternal injection of the synthetic double-stranded RNA polyinosinic-polycytidylic acid causes a prepulse inhibition deficit in the offspring in the absence of virus. Therefore, maternal viral infection has a profound effect on the behavior of adult offspring, probably via an effect of the maternal immune response on the fetus.

Summary

This review discussed the incidence of influenza in virally infected mothers and its association with the development of schizophrenia. What is clear is that the relationship between influenza virus and schizophrenia is still incompletely understood. In human studies, research remains contradictory. In animal studies there is evidence of disruption of programmed maturation of the brain and

GFAP = glial fibrillary acidic protein

subsequent behavioral abnormalities following viral exposure in pregnancy. The early brain anomalies created by such disruption increase the vulnerability to the onset of disorder abnormalities during late adolescent and early adulthood. The identification of infection risk factors for schizophrenia may translate into new insights into the pathogenesis of schizophrenia.

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Capsule

Unraveling Werner syndrome

Werner syndrome (WS) patients suffer many symptoms of premature aging, including wrinkled skin, graying hair and hair loss, osteoporosis, heart disease, and cataracts. Cells from WS patients enter senescence prematurely, show increased rates of genome instability, and rapidly lose their telomeres – the protective ends of their chromosomes. The WRN helicase, mutated in WS, is involved in the maintenance of the telomeres, possibly through the untangling of "knotty" (G-quadruplex) DNA.

Crabbe et al. found that the WRN helicase is associated with telomeric DNA during S-phase of the cell cycle. Loss of WRN helicase activity leads to the loss of telomeres from single sister chromatids, and only telomeres replicated by lagging-strand DNA synthesis are affected.

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