Prenatal Influenza Infections and Adult Schizophrenia

by Sarnoff A. Mednick, Matti O. Huttunen, and Ricardo A. Machón

Abstract

We reported previously that residents of Greater Helsinki, Finland, whose mothers were exposed to the 1957 influenza epidemic during their second trimester of gestation had a significantly elevated risk of developing adult schizophrenia. The majority of the replication studies to date have not determined whether the mothers actually contracted an infection or the stage of gestation based on mother's last menstruation. We read prenatal clinic records of the mothers of the Helsinki-born schizophrenia subjects to determine timing of infection, as noted by the prenatal clinic obstetric nurse at a time close to the actual infection. Schizophrenia subjects who were exposed in the second trimester had a significantly higher rate of definite influenza infection (86.7%) in that period compared to those who were exposed during the first and third trimesters (20.0%). These results are interpreted with caution because of the small number of cases.


We reported previously that residents of Greater Helsinki who were exposed to the 1957 influenza epidemic during their second trimester of gestation had a significantly elevated risk for schizophrenia (Mednick et al. 1988). Successful replication of this finding has been reported for England and Wales (O’Callaghan et al. 1991a). Kunugi and colleagues (1992) reported a significant increase of schizophrenia in individuals whose sixth month of fetal gestation overlapped the peak of the 1957 epidemic in Tokyo. Waddington (1992) also reported a replication of the second-trimester effect in Ireland. Additionally, in a southern hemisphere replication, McGrath (personal communication, December 1992) found an increase of schizophrenia in individuals exposed to the same 1957 influenza epidemic in their second trimester of fetal life in a sample from Brisbane, Australia.

A study of the aftermath of the 1957 influenza epidemic in the city of Edinburgh also reported a second trimester (sixth month) effect for schizophrenia (Kendell and Kemp 1989). When the authors examined data for Scotland they reported a failure to replicate. A reanalysis of their published data, however, revealed a significant second-trimester effect (Mednick et al. 1990b). Furthermore, in an extension of the Helsinki study encompassing all of Finland (Machón and Mednick, in press), the second-trimester effect for the 1957 influenza epidemic was replicated again.

Crow and Done (1992) reported on a study of individuals born March 3-9, 1958 (after the 1957 epidemic). They failed to find a relationship between maternal report, at the time of delivery, of influenza infection during pregnancy and adult schizophrenia diagnosis in their offspring. This study has been criticized because of the low number of cases identified in their sample, which may compromise the statistical power

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of the design. Crowe and Done (1992) reported in their sample a narrow definition of schizophrenia as 4 out of 1,851 or 2.1 per 1,000, and a broad definition as 7 out of 1,851 or 3.8 per 1,000. The rates of schizophrenia at age 26.2 years for those in our Helsinki study who were born in 1957-58 ranged between 5.8 and 11.6 per 1,000 live births (Mednick et al. 1988). In addition, the rate of influenza infection reported (1.4%-5.8%) cannot be reconciled with the rate of influenza infection (28.0%) reported for women of childbearing age in this area (O’Callaghan et al. 1991b). While the rates for entire countries like England, Scotland, and Wales might be expected to be lower than rates in a large metropolitan area like London, it is difficult to reconcile such a large reduction in infection rates in the sample reported from the National Child Development Study (Atkins et al. 1981; Fogelman and Wedge 1981). Moreover, selecting cases born during 1 week in March introduces some biases. These problems have been recognized and discussed by the authors of the 1946 British Birth Cohort, which also sampled individuals born in the United Kingdom March 3-9, 1946 (Atkins et al. 1981; Fogelman and Wedge 1981).

Bowler and Torrey (1990) briefly report a study covering 10 States in the United States. They failed to detect an association between second-trimester exposure and adult schizophrenia. In an earlier study in two States, Torrey and colleagues (1988) also attempted to replicate the second-trimester findings but had inconsistent results. In neither of these two studies could the authors identify the subjects’ place of birth. This may be a serious problem in the United States because of the high rates of mobility and immigration. Some of the individuals with schizophrenia may have been born in States or countries other than those studied. For such subjects, the viral disease frequencies and timing data for these States may be less relevant.

Two studies have reported on risk for schizophrenia following exposure to influenza epidemics other than the one in 1957. Studies from Denmark (Barr et al. 1990) and England (Sham et al. 1992) have examined the risk of schizophrenia for those exposed to influenza infection during fetal development. In Denmark, Barr and colleagues (1990) examined the psychopathological aftermaths of 40 years of influenza epidemics; in England, Sham and colleagues (1992) studied the aftermaths of 22 years of influenza epidemics. In both of these studies it was noted that exposure to an epidemic during the second trimester of fetal development significantly increased risk of adult-onset schizophrenia.

These findings have been interpreted as suggesting that a maternal influenza infection during gestation may have resulted in a disruption of fetal neural development, which produced neurointegrative deficits, which in turn increased risk for adult schizophrenia (Mednick 1988). The idea that some part of the etiology of schizophrenia may have its roots in errors of fetal neural development has assumed an important position in this field (Mednick et al. 1991b). All the studies cited except Crow and Done (1992) have two methodologic problems, which the current study addresses. The first problem is that in the studies cited, the increased risk for schizophrenia was related only to second-trimester exposure to the epidemic, that is, the temporal overlap of the second trimester of gestation with the height of the epidemic. None of the studies determined whether the mothers actually contracted an infection. To determine whether any of the mothers actually experienced a viral infection, we examined Helsinki prenatal clinic files for each of the 71 schizophrenia patients exposed to the 1957 Helsinki epidemic during their first, second, or third trimesters of gestation.

The routine forms contain an item inquiring about infections during pregnancy. The second problem with the studies cited is that the fetus’ gestational stage at the time of the epidemic has been estimated from date of birth. For pre- and postterm babies, this estimate would be incorrect. Since individuals with schizophrenia tend to be born prematurely and with low birth weight (Mednick et al. 1991a), this method of estimation could result in assignment of subjects to an inappropriate trimester of exposure to the epidemic. In the current study, we determined stage of gestation from the expected date of delivery which, in turn, was based on the date of the mother’s last menstruation. Both of these pieces of information are included in the prenatal clinic records.

In the Helsinki study (Mednick et al. 1990a), 8.7 per 1,000 of those exposed in the first trimester, 14.1 per 1,000 of fetuses exposed in the second trimester, and 7.4 per 1,000 of those exposed in the third trimester became ill with schizophrenia by age 29.8 years. The corresponding raw number of cases of schizophrenia in each of the trimesters of exposure was 18, 33, and 20. That we find schizophre-
nia in individuals who were not exposed in the second trimester illustrates that second-trimester exposure to the 1957 epidemic is only one of many possible agents that may increase risk for schizophrenia. Thus, the group of 33 schizophrenia patients exposed during the second trimester is composed of those who would have become ill with schizophrenia even if there had not been an epidemic and those "surplus" cases whose schizophrenia is associated with an influenza infection their mother suffered during their second trimester of gestation. This leads to the prediction that the rate of recorded influenza-induced schizophrenia will be significantly higher for the 33 second-trimester schizophrenia patients than for the 38 schizophrenia subjects exposed in the first and third trimesters.

In this study, we examined the population of schizophrenia patients born to Helsinki residents in the 9 months following the 1957 influenza epidemic. As noted above, this population of schizophrenia subjects was divided into three exposure groups on the basis of the period of gestation that overlapped the 1957 Helsinki influenza epidemic. We hypothesize that the rate of prenatally recorded influenza infections will be higher among the mothers of schizophrenia subjects exposed during their fetus' second trimester of gestation than among the mothers of individuals with schizophrenia exposed during their fetus' first or third trimester. Thus, the rate of influenza infection for individuals exposed during the first and third trimesters should be approximately the same as the population rate for the epidemic (23%-30%) (Hakosalo 1973), while the rate for the second-trimester-exposed should be significantly higher.

Methods

Almost all expectant women in Finland attend free prenatal maternity clinics (and did so also in 1957-58). In Helsinki, the prenatal clinics are spread across the city, making visits very convenient. Most women visit regularly; frequency of visits depends on the stage and course of the pregnancy. As noted, the routine form completed by the attending obstetrical nurse for each visit to the prenatal clinic includes an item on infections. If an infection is recorded in the files, it is almost certain that some illness was present. The frequent visits would reduce failure to report infections, but less severe infections occurring 1 to 2 weeks before a visit may not have been reported. We anticipated some degree of underreporting of infections, but this problem is likely to be equally distributed among the three trimesters.

The 1957-58 files of the city of Helsinki prenatal clinics are centrally stored. From the group of 71 schizophrenia subjects born in greater Helsinki (Uusimaa County), we selected the records of those born to residents of the city of Helsinki because their prenatal records could be easily located in the central storage files. There were a total of 50 Helsinki cases, 25 of which were located in the files. The 25 missing files represent a troublesome amount of missing data, but their absence is understandable given the procedures followed in Helsinki. Generally, the file from the prenatal clinic is given to the expectant mother to bring to the obstetrical hospital. From the hospital, the file is brought by the mother to the pediatric clinic. When the child starts school, the file is added to the school health record. If the family moves to a suburb of Helsinki, which has been quite common in the past 10 years, the prenatal clinic records go with them and are retained by the community to which they moved. The 25 records we found thus belonged to individuals whose families had not moved from the city of Helsinki during their school years. While this selection may bias some characteristics of the located subjects, it is difficult to imagine why women whose family moved to the suburbs during their child's school years would be more likely to have suffered an influenza infection during the 1957 epidemic and during their fetus' second trimester of gestation.

We read the 25 records that were located to determine which of the mothers of the individuals with schizophrenia exposed in the first, second, and third trimester had been noted by the obstetrical nurse to have suffered an influenza infection. Cases were counted as an influenza infection if characteristic upper respiratory symptoms and fever were recorded. The obstetrical nurse almost always recorded a single date for the infection, along with the symptoms. It was not clear from the records whether this was the beginning or the ending date of the illness, which usually lasted at least 1 week. We used the date recorded by the obstetrical nurse to place the time of the infection relative to the individual's trimester of development. As noted, the prenatal maternity clinic form includes the expected date of delivery, based
on the date of the last menstruation. The expected date of delivery was used to calculate the stage of gestation the fetus had reached at the time of the mother's influenza infection.

From each schizophrenia patient's expected date of delivery, we determined his or her trimester of exposure to the epidemic. (Three schizophrenia subjects previously categorized as having been exposed during their seventh month of gestation had actually been exposed during their sixth month of gestation.) For each individual with schizophrenia whose mother was noted to have had an influenza infection, we established the trimester of gestation at the time of the infection. This permitted us to calculate, for each trimester of exposure, the percentage of schizophrenia patients whose mothers had an influenza infection.

Results

In the second trimester, 86.7 percent (13 of 15) of the schizophrenia subjects exposed had a definite influenza infection in that period; 20 percent (2 of 10) of those exposed in the first and third trimesters had a definite influenza infection during those two trimesters. The differences are statistically significant (Fisher's Exact Test, \( p = 0.003 \)); the hypothesis is supported. The rate of definite influenza infection for individuals with schizophrenia exposed during the second trimester of gestation is significantly higher than the rate in the other two trimesters.

We examined some characteristics of the missing subjects to determine whether they were different on any sociodemographic or diagnostic measure from the subjects for whom we have data. The characteristics examined were as follows: age and diagnostic status of the mother, socioeconomic status, pregnancy, labor and birth complications, employment status of the mother, and number of older children. The missing subjects were highly similar to the located subjects on these measures; no significant differences were noted. We also compared the located second trimester subjects \( (n = 15) \) with the located first and third trimester subjects \( (n = 10) \) on the characteristics mentioned above. No significant differences were noted, but there was a trend for second trimester schizophrenia subjects to have suffered fewer obstetrical complications.

Discussion

These results support the assertion that the increased rate of schizophrenia among the fetuses exposed to the Helsinki epidemic in their second trimester of gestation is associated with a significantly elevated rate of definite influenza infection. In view of the growing importance of the neurodevelopmental hypothesis as a viable theory of schizophrenia etiology and the seminal role of the viral studies in supporting this theory, these findings encourage inquiry into the direct and indirect mechanisms by which an influenza infection during a critical stage of gestation increases risk for adult schizophrenia.

Although the sample available for this analysis is small, we are presenting these data because the differences observed between the first and third trimesters and the second trimester are considerable, and data from the Finnish prenatal clinics are an unusual resource. A replication of the study in another appropriate national setting is, of course, warranted.

References


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