

Prenatal Infection as a Risk Factor for Schizophrenia

Alan S. Brown^{1,2}

²College of Physicians and Surgeons, Columbia University; New York State Psychiatric Institute, Columbia University, New York, NY; and Mailman School of Public Health, Columbia University, New York, NY

Accumulating evidence suggests that prenatal exposure to infection contributes to the etiology of schizophrenia. This line of investigation has been advanced by birth cohort studies that utilize prospectively acquired data from serologic assays for infectious and immune biomarkers. These investigations have provided further support for this hypothesis and permitted the investigation of new infectious pathogens in relation to schizophrenia risk. Prenatal infections that have been associated with schizophrenia include rubella, influenza, and toxoplasmosis. Maternal cytokines, including interleukin-8, are also significantly increased in pregnancies giving rise to schizophrenia cases. Although replication of these findings is required, this body of work may ultimately have important implications for the prevention of schizophrenia, the elaboration of pathogenic mechanisms in this disorder, and investigations of gene-environment interactions.

Key words: infection/virus/schizophrenia/prenatal/epidemiology

Evidence supporting the hypothesis that prenatal infection plays a role in the etiology of schizophrenia is increasing. This article focuses on recent work from our group and others which has demonstrated that gestational exposure to influenza, other infections, and elevations of specific pro-inflammatory cytokines are associated with an increased risk of schizophrenia. In these investigations several methodological advantages have been brought to bear on informative birth cohorts and have helped to support and extend this hypothesis. These design advantages include prospective data using biomarkers on infection in maternal serum samples and direct assessment of cases.

Specific Prenatal Infections and Inflammatory Biomarkers Implicated in Schizophrenia

Rubella

Prenatal rubella is a well-known central nervous system teratogen and possibly is a cause of some childhood psychiatric disorders.¹ We therefore hypothesized that this infection might also increase risk for adult schizophrenia. To test this hypothesis, we examined the risk of schizophrenia in members of a cohort in New York City who were born to mothers with clinical rubella, which was serologically confirmed. We found that 20% of prenatally rubella-exposed subjects were diagnosed with adult schizophrenia, suggesting a 10 to 20-fold increase in risk.² A decline in IQ between childhood and adolescence in this cohort was highly predictive of schizophrenia in the offspring.

Influenza

Among the in utero infections that are plausible risk factors for schizophrenia, influenza has been the most commonly examined. In a seminal study, Mednick et al.³ demonstrated an increase in risk of schizophrenia among Finnish individuals who were in the second trimester of fetal development during the 1957 A2 influenza pandemic; however, over 25 subsequent studies reported inconsistent findings,⁴ leading investigators to question the viability of the hypothesis.

Although these studies were groundbreaking, a significant limitation was the reliance on ecologic data to define influenza exposure, such that individuals were considered to have been influenza-exposed based only on having been in utero during one or more influenza epidemics. Since most were not influenza-exposed, this led to nondifferential misclassification of exposure, which may bias the effect toward the null. To address this limitation, we obtained serologic measures of antibody status in individual pregnancies to document influenza, then related the exposure to risk of schizophrenia in offspring using direct, research-based interviews.⁵ The sample was derived from the Prenatal Determinants of Schizophrenia Study based on a large and well-characterized birth cohort in northern California that was followed up for schizophrenia.⁶ We found that serologically documented influenza exposure during early to mid-gestation was associated with a 3-fold increased risk of schizophrenia; first trimester exposure to influenza conferred a 7-fold increased risk.⁵

¹To whom correspondence should be addressed; e-mail: asb11@columbia.edu.

Toxoplasmosis

Like rubella, *Toxoplasma gondii*, a ubiquitous intracellular parasite, is a well-known central nervous system teratogen.⁷ We investigated whether elevated maternal antibody to this infection was related to onset of schizophrenia in adult life. Using bioassays on maternal archived serum from the same northern California birth cohort as in the influenza study described above, we demonstrated that elevated maternal toxoplasma IgG antibody was associated with a 2 1/2-fold increase in risk of schizophrenia.⁷

Herpes Simplex Virus Type 2 (HSV-2)

In another birth cohort, Buka et al.⁸ found elevated maternal IgG antibody to HSV-2 in offspring who later developed psychotic disorders, including schizophrenia. In a larger sample consisting exclusively of schizophrenia and schizophrenia spectrum disorder cases, however, we were not able to replicate this finding.⁹

Cytokines

Cytokines and chemokines are known to mediate the host response to infection and thus might explain associations between different prenatal infections and schizophrenia. In our birth cohort study in northern California, we demonstrated that second-trimester maternal levels of the chemokine interleukin-8 (IL-8) were nearly twice as high for offspring who later developed schizophrenia, compared with controls. In a smaller sample an association was demonstrated between maternal TNF- α and psychotic disorders among offspring.¹⁰

Interpretation and Limitations of the Findings

These findings have provided the strongest evidence to date that prenatal infection contributes to risk for schizophrenia. They must, however, be viewed with caution. First, there have yet to be attempts to replicate most of these results in the published literature. Second, the mechanisms by which these infections might lead to schizophrenia have not been well delineated. Potential mechanisms include teratogenic effects of maternal antibodies on neurodevelopment and a surge in circulating cytokines. Recent animal models suggest that influenza and immune activation have effects on the fetal brain that appear to be concordant with findings observed in schizophrenia.¹¹

With regard to toxoplasmosis, an increase in IgM antibody, an indicator of recent infection, was not found; thus, the observed increase in IgG antibody may have resulted from an infection occurring months or years prior to the measurement. Nonetheless, since toxoplasma remains in a latent, sequestered state for many years following infection, it is conceivable that suppressed reactivation of this parasite by a chronic maternal immune

response, rather than the organism itself, may be responsible for the association.

The reasons for the association between second-trimester IL-8 and schizophrenia are also unclear, in part because the many roles of this chemokine are still under investigation. Among its known functions, IL-8 is involved in the adherence of neutrophils to endothelial cells and in free radical formation.¹² Nonetheless, the plausibility of IL-8 as a risk factor for schizophrenia is supported by the fact that this chemokine has been associated with chorioamnionitis in infants born at term, and a significant correlation has been observed between maternal and neonatal serum IL-8 levels.

A third limitation is that we have yet to investigate whether these infections and immune disturbances act in concert with one another to increase schizophrenia risk. This work is underway.

Future Directions

We wish to highlight 3 potential implications of this work for future research and interventions. First, it is important to test the plausibility of this hypothesis and to identify pathogenic mechanisms by which these infections increase schizophrenia risk. This can be addressed by translational approaches, such as that noted above for influenza, and by clinical studies, which we have been conducting, that aim to relate prenatal infection to brain anomalies that have been observed in adult patients with schizophrenia.

Second, we believe that it is essential for future work to investigate interactions between prenatal infection and susceptibility genes. Given that the effect sizes observed have been moderate, it is likely that prenatal infection increases risk of schizophrenia only among subgroups of vulnerable individuals, including those who are genetically predisposed or who have been exposed to other environmental factors. This work could help to provide a more complete picture of disease causation and potentially aid in the identification of vulnerability genes.

Finally, studies of prenatal infection and schizophrenia may hold considerable promise for preventive efforts. Our data on influenza indicated that as many as 14% of schizophrenia cases would not have occurred if influenza infection during early to mid-gestation had been prevented.⁵ This may have important public health implications, given that there are many available preventive strategies for influenza and other infections, including vaccination, antibiotics, and simple hygienic measures.

In summary, our data thus far suggest that several prenatal infections and inflammatory biomarkers may contribute to the etiology of schizophrenia. It must be emphasized, however, that these findings require replication in independent samples before any specific public health measures are recommended. Nonetheless,

the study of prenatal infection in schizophrenia promises to play an important role in revealing at least some of the biological underpinnings of this devastating disorder.

Acknowledgments

This manuscript was supported by the following grants: NIMH 1R01MH 63264-01A1 (A.S.B.), NIMH 1R01MH06249 (A.S.B.), NIMH 1K02MH65422-01 (A.S.B.), a NARSAD Independent Investigator Award (A.S.B.), NICHD N01-HD-1-3334 (B.A. Cohn), and NICHD N01-HD-6-3258 (B.A. Cohn). We wish to acknowledge the following individuals for their contributions to this work: Ezra S. Susser, M.D., Dr.P.H., Catherine A. Schaefer, Ph.D., Barbara van den Berg, M.D., Barbara Cohn, Ph.D., Michaeline A. Bresnahan, Ph.D., Charles P. Quesenberry Jr, Ph.D., Liyan Liu, M.D., M.Sc., the late Jacob Yerushalmy, M.D., Gilman Grave, M.D., Roberta Christianson, M.A., and Justin Penner, M.A. We also wish to thank the National Institute for Child Health and Development and the Public Health Institute, Berkeley, Calif.

References

1. Chess S, Korn S, Fernandez P. *Psychiatric Disorders of Children with Congenital Rubella*. New York, NY: Brunner/Mazel; 1971.
2. Brown AS, Cohen P, Harkavy-Friedman J, et al. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biol Psychiatry*. 2001;49:473-486.
3. Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1988;45:189-192.
4. Bagalkote H. Maternal influenza and schizophrenia in the offspring. *Int J Ment Health*. 2001;29:3-21.
5. Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence for prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61:774-780.
6. Susser ES, Schaefer CA, Brown AS, Begg MD, Wyatt RJ. The design of the Prenatal Determinants of Schizophrenia Study. *Schizophr Bull*. 2000;26:257-273.
7. Brown AS, Schaefer CA, Quesenberry CP Jr, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry*. 2005;162:767-773.
8. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry*. 2001;58:1032-1037.
9. Brown AS, Schaefer CA, Quesenberry CP, Jr., Shen L, Susser ES. No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia. *American Journal of Psychiatry*. In press.
10. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. Maternal cytokine levels during pregnancy and adult psychosis. *Brain Behav Immun*. 2001;15:411-420.
11. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci*. 2003;23:297-302.
12. Brown AS, Hooton J, Schaefer CA, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. *Am J Psychiatry*. 2004;161:889-895.