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Maternal Infection and Schizophrenia: Implications for Prevention

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Accumulating evidence suggests that maternal infection is a risk factor for schizophrenia. Prospective epidemiological studies indicate that maternal influenza, toxoplasmosis, and genital/reproductive infection are associated with this disorder in offspring. Preclinical models of maternal immune activation have supported the neurobiological plausibility of these microbes in schizophrenia. Previous studies suggest that treatment or prophylactic efforts targeting these and other infections could have significant effects on reducing the incidence of schizophrenia, given that they are common in the population and the effect sizes derived from epidemiological studies of these and other microbial pathogens and schizophrenia, to date, are not small. Fortunately, the occurrence of many of these infections can be reduced with relatively practical and inexpensive interventions that are scalable to large populations given adequate resources. Hence, in the present article, we focus on the potential for prevention of schizophrenia by control of infection, using these 3 categories of infection as examples. Lessons learned from previous successful public health efforts targeting these infections, including the relative advantages and disadvantages of these measures, are reviewed.

Key words: influenza/environment/neurodevelopment/epidemiology/genital reproductive infection/toxoplasmosis

Introduction

Accumulating data from epidemiological studies have implicated maternal infection in the etiology of schizophrenia. Infection is an especially appropriate candidate risk factor for this theme issue of *Schizophrenia Bulletin* focused on prevention because it is a prototype of an exposure for which preventive interventions have been implemented on a large scale with great success in eradication and control.

Maternal infection is generally regarded as 1 of the more plausible risk factors for schizophrenia, given that microbial pathogens have been clearly documented to cause congenital brain anomalies and a variety of learning and behavioral disorders in childhood. It has been known for many years that subjects exposed to rubella, toxoplasma, herpes simplex virus type 2 (HSV-2), and other infections during pregnancy are at substantially increased risk of neurodevelopmental disorders, including mental retardation, learning disabilities, sensorineural dysfunction, and structural brain anomalies.[1]

Initial Studies of Maternal Exposure to Infection and Schizophrenia

Although investigators had earlier hypothesized that infectious microbes may play a role in the etiology of schizophrenia, the first empirical test of this hypothesis did not occur until the late 1980s (reviewed in detail by Brown and Derkits[2]). Initial studies assessed whether the occurrence of influenza epidemics in populations were correlated with schizophrenia births among those in utero during the epidemics. Although initial studies suggested an increased occurrence of schizophrenia among individuals who were in utero during influenza epidemics during the second trimester,[3,4] some subsequent studies, with generally larger case samples and more complete ascertainment of schizophenia, failed to replicate these results.[5,6] A further review and critique of these studies can be found in Selten et al.[7] Ecological studies of other infections, including maternal respiratory viral infections,[8,9] measles, varicella-zoster,[9,10] mumps,[9] and polio,[11] have yielded positive evidence of associations with schizophrenia.

These studies were hampered, however, by a number of methodological limitations, including a high rate of misclassification of exposure due to use of ecological data on infection, a lack of documentation of infection in individual pregnancies, and assumption of a full-term

pregnancy. Each of these limitations tends to bias findings toward the null and may explain the inconsistencies in the previous findings. Hence, in our view, it is probably not productive to proceed with further ecological studies to address the question of prenatal infection and schizophrenia.

Birth Cohort Studies of Maternal Infection and Schizophrenia

These methodological shortcomings were the prime motivator for our group and others to initiate birth cohort studies aimed at refining the methodology for testing the infection-schizophrenia hypothesis.[2] The study of subjects who were born during a particular period and geographic region, in whom exposure to infection during pregnancy could be acquired, yielded a number of methodological advantages, including prospectively documented maternal infection in individual pregnancies, longitudinal follow-up, accurate assessment of the timing of infection during pregnancy, and control of potential confounding factors. The use of archived biological specimens from the mother or infant has allowed investigators to further capitalize on these birth cohorts because they permit the measurement of biomarkers of infection during pregnancy.

These studies have yielded a series of intriguing associations (reviewed in Brown and Derkits[2]) and are briefly summarized here. Our group demonstrated that prenatal exposure to rubella was related to a greater than 5-fold increased risk of nonaffective psychosis during young adulthood[12] and in midadulthood over 20% of subjects who were exposed in utero to rubella were diagnosed with schizophrenia or a schizophrenia spectrum disorder.[13] Influenza exposure documented by quantification of maternal antibody titers during pregnancy was associated with a 3-fold increased risk of schizophrenia for exposure in mid to late gestation and a 7-fold elevation in risk of the disorder following first trimester exposure.[14] Elevated maternal IgG antibodies to *Toxoplasma gondii*, an intracellular parasite and a well-known infectious cause of central nervous system (CNS) congenital anomalies,[1,15] was related to greater than 2-fold increased risk of schizophrenia,[16] a finding which was essentially replicated in a Danish sample that capitalized on filter paper blood spots taken from the infant within the first week of birth.[17] In 3 studies, elevated maternal IgG antibody to (HSV-2) was related to an increased risk of psychotic disorders, including schizophrenia,[18,19,20] while the finding was not replicated in a different birth cohort.[21] Maternal genital/reproductive infections, broadly defined, were, however, associated with a 5-fold increased risk of schizophrenia when the exposure occurred during the periconceptional period.[22] Exposure to maternal respiratory infection was related to a 2-fold elevated schizophrenia risk,[23] as well as bacterial infections broadly defined.[24]

In summary, birth cohort studies have provided several key methodological advantages that have allowed for more rigorous testing of relationships between maternal infection and schizophrenia. Birth cohort studies conducted to date have provided further support for the hypothesis that maternal viral, protozoal, and bacterial infections increase the risk for schizophrenia in adult offspring.

Cytokines

One question that is currently being addressed relates to the mechanisms by which maternal infection increases schizophrenia risk. Some infections, particularly rubella and certain genital/reproductive microbes, are known to cross the fetal blood-brain barrier because they have been isolated from fetal brain. Pathogenic mechanisms by which these infections alter fetal neurodevelopment have been described.[1] It has become increasingly clear, however, that many of the infections studied in relation to schizophrenia may act by indirect mechanisms. One of the most widely studied of these mechanisms involves the release of maternal cytokines in response to infectious insults. These proteins can traverse the placenta and fetal blood-brain barrier and have a variety of effects on fetal brain development.[25] Of particular relevance to schizophrenia are findings from animal models of the maternal infection risk factor. In 1 mouse model, maternal infection is mimicked by injection of poly(I:C), a synthetic double-stranded RNA that stimulates the maternal immune system as if there had been a viral infection. A related rat model involves injection of lipopolysaccharide to mimic the effects of a maternal bacterial infection.

In the poly(I:C) maternal immune activation (MIA) model, the adult offspring exhibit a series of behavioral abnormalities that are consistent with those seen in schizophrenia (eg, increased anxiety and hyper-responsivity to glutamatergic and dopaminergic stimuli as well as deficits in social interaction, working memory, prepulse inhibition, and latent inhibition). The adult offspring also display neuropathology characteristic of schizophrenia (eg, enlarged ventricles and spatially restricted deficits in parvalbumin-immunoreactive interneurons) (reviewed by Meyer and Feldon[26] and Patterson[27]). Exploring potential mediators of the effects of maternal infection, Smith et al[28] found that the cytokine interleukin-6 (IL-6) is required for the effects of MIA on fetal brain development. In this study, antibody to IL-6, which neutralizes the effect of IL-6, resulted in a reversal of the behavioral and brain effects induced by poly I:C in mice. In addition, the offspring of mothers in which the IL-6 gene was removed showed none of these brain or behavioral effects. Moreover, the behavioral deficits seen with poly(I:C) MIA can be mimicked by a single maternal injection of IL-6.[28] Downstream of the IL-6 receptor, activation of IL-6 response genes is found both in the

placenta and in the fetal brain, and IL-6 messenger RNA is induced as well, raising the possibility of a positive feedback cycle to maintain inflammation.[29]

Brown et al[30] demonstrated that maternal second and early third trimester exposure to elevated interleukin-8 (IL-8), a proinflammatory chemokine, was related to an increased risk of schizophrenia, with maternal levels of IL-8 approximately 2-fold higher in cases than controls. In a study of cytokines and schizophrenia from another birth cohort, maternal perinatal levels of tumor necrosis factor-α, a proinflammatory cytokine, were increased for cases with psychotic disorders.[31]

Although cytokines represent a leading candidate agent for the effect of infection on schizophrenia risk, other possible mediators include hyperthermia, which is teratogenic to animals[32]; fetal hypoxia, which has been associated with schizophrenia[33,34]; and over the counter remedies taken for influenza such as aspirin, which has been associated with anomalies of the CNS.[35]

Prevention

If prenatal infection becomes established as a risk factor for schizophrenia, this would have considerable implications for prevention of this illness, given that many approaches aimed at preventing and treating infections are well integrated into public health programs. The population attributable risk (PAR) is an estimate of the effect on disease occurrence by removal of a causative exposure. The PAR is determined by the magnitude of the effect of the risk factor and by the population prevalence of the risk factor.[36] Several of the infections that have been implicated in schizophrenia, including influenza, *T. gondii*, and genital/reproductive infections, are highly prevalent in the United States and global populations.

Brown and Derkits[2] demonstrated that the PAR for exposure to these 3 maternal infections is approximately 30% (The PAR was calculated as $RR-1P_1/RR$, where RR indicates the relative rate and P_1 is the proportion of exposed cases. In accordance with the usual practice for case-control studies, we substituted the adjusted odds ratio for the RR.) Based on this result, their prevention in the pregnant population in our sample would reduce the number of schizophrenia cases by about one-third. One should keep in mind, however, that this figure may have been overestimated if the true effect size was smaller. Moreover, the population prevalences of these exposures may vary between populations. It is also worth noting, however, that this figure does not include bacterial infections, which may also be risk factors, nor does it include many other microbial infections that have not been investigated in relation to schizophrenia. Thus, the 30% figure could be an underestimate.

In the following section, we describe previous efforts to control these 3 infections, which have been implicated in schizophrenia and their potential relevance to the prevention of this disorder.

Influenza

Vaccination has become a mainstay for the prevention of influenza. It is a safe and effective approach that has prevented millions of cases and saved tens of thousands of lives, particularly among vulnerable populations. Each year, new vaccinations must be developed due to ongoing mutations in influenza strains (antigenic drift) and occasional changes in influenza serotypes (antigenic shift).[37] Substantial progress has been made to expedite the development of influenza vaccines, as demonstrated by the response among the scientific community to the recent H1N1 "swine flu" epidemic. Advances in identification of the genomic and antigenic sequences of these viruses were a major factor in development of the H1N1 vaccine, contributing to successful control of the epidemic.

Some evidence suggests that pregnant women represent a high-risk group to be targeted for influenza vaccination given potential effects on fetal morbidity and mortality.[38] In a recent review, the risks and benefits of maternal influenza and of influenza vaccination were extensively discussed.[39] Evidence for increased morbidity, including cardiopulmonary hospitalization, secondary to influenza during healthy human pregnancy is conflicting, with some studies demonstrating an elevation during the second trimester and later in pregnancy,[40] while other studies failed to demonstrate a clear effect during any period of pregnancy[41]; concurrent physical illnesses increase the likelihood of complications of influenza infection during pregnancy. With regard to mortality from influenza during pregnancy, the only convincing evidence of an increase derives from studies of influenza pandemics,[42,43] while interpandemic maternal mortality appears to be low.[44]

There is no clear evidence that immediate pregnancy outcomes in the fetus are associated with maternal influenza, with no increase in preterm delivery, low birth weight, low Apgar scores, or specific congenital anomalies (see review by Skowronski and De Serres[39]), the only exception being an increase in fetal loss during the 1918–1919 pandemic.[45] Although there are no randomized clinical trials (RCTs) with laboratory-based outcomes of influenza vaccination, some, though not all, observational studies suggest a trend for fewer episodes of acute respiratory illness among pregnant vaccinated women.[46,47] The only known RCT indicated that infants of immunized mothers had a reduction in laboratory-confirmed influenza infection.[38]

Few studies have evaluated the safety of influenza vaccination during pregnancy on offspring outcomes. In the Collaborative Perinatal Project, a large birth cohort, no increase in fetal malformations or mortality to age 4 was observed among offspring of mothers who received

influenza vaccination during pregnancy,[48,49] and C-section and preterm labor were not increased in another cohort analysis.[47] It is worth noting, however, that none of these studies included long-term follow-up for physical or mental health conditions.

In conclusion, there is some evidence that influenza infection during pregnancy may increase risk of medical complications in the mother and that vaccination may reduce the occurrence of maternal respiratory illness and risk of influenza in the infant. Although there are no clear adverse effects of influenza vaccination on perinatal complications and malformations in the offspring, there is a notable lack of long-term data on the potential protective and detrimental effects of influenza vaccination in the offspring.

Current recommendations, by several organizations including the Centers for Disease Control and the American College of Obstetricians and Gynecologists, include universal influenza vaccination to pregnant women. Given that the increased risk of schizophrenia among subjects whose mothers were exposed to influenza in early to mid-pregnancy may have been due to the cytokine response to infection, it is conceivable that MIA induced by influenza vaccination may have detrimental effects. It is also worth noting that in rodent studies of the maternal infection risk factor for schizophrenia, activation of the maternal immune system, in the absence of pathogen, is sufficient to yield offspring with schizophrenia-like features.[27] Because vaccination also stimulates the maternal immune system these animal studies also raise questions about universal vaccination during pregnancy. Although the immune stimulation from a significant infection would certainly be greater than that from a vaccination, there is a considerable variability in individual responses to vaccination.

Hence, further research, particularly birth cohort studies with long-term follow-up, and translational studies aimed at evaluating the maternal cytokine response and subsequent fetal outcomes following vaccination, are necessary. In our view, until these studies are conducted, 1 prudent approach is to vaccinate pregnant women with a comorbid condition that may threaten the health of the fetus and to immunize nonpregnant women of reproductive age.[14]

Toxoplasma gondii

Prevention of *T. gondii* infection is based on control of the main sources of the parasite. Humans become infected by ingesting soil or water contaminated with oocysts, from tissue cysts in undercooked meat, and other less common means.[50] Direct contact with cats does not appear to pose a significant risk of infection in humans,[51,52] in spite of a high seroprevalence of *T. gondii* in felines, given that oocysts are not infective when passed, and the duration of oocyst shedding is short. Although it is still prudent to take adequate precautions to guard against exposure to *T. gondii* when changing cat litter boxes, these findings suggest that measures other than avoidance of cats will have a greater effect on reducing exposure to this pathogen. Common recommendations include the use of gloves while gardening or having other interactions with soil and hand washing after these activities. Adequate cooking of meat before consumption (1 h at 50°C) or higher temperatures for briefer periods inactivates *T. gondii* tissue cysts; however, cooking infected meat in microwave ovens does not guarantee killing of the parasite.[53] It has also been demonstrated that freezing meat for 2 days at −20° C is sufficient to inactivate the parasite. Changing other consumer cooking habits, such as washing kitchen knives after cutting meat, fruits, and vegetables, and frequent hand washing, may also have an important impact on reducing *T. gondii* exposure.

It is worth underscoring the point that schizophrenia was related in the previously reviewed studies to elevated anti-*T. gondii* IgG antibodies.[16,17] It is expected that only a small minority of these infections were acquired during pregnancy, given the relative low incidence of primary *T. gondii* infection, suggesting that most infections were acquired before pregnancy. Consequently, the above recommendations would need to be initiated long before reproductive age and should ideally be applied universally. Nonetheless, the relative practicality and lack of expense of many of these preventive measures offer cause for optimism and may account for the considerable decline in seroprevalence of *T. gondii* in the United States, from 14.1% among persons aged 12–49 years in 1988–1994 to 9.0% in this age group from 1999 to 2004.[54]

Genital-Reproductive (G/R) Infections

G/R infections represent a significant challenge to global health because they are highly prevalent, particularly in the reproductive-aged population, and can lead to substantial disability. Consequently, numerous efforts have been made to prevent (and treat) these infections, although with varying levels of success. The prevention of G/R infections, most of which are sexually transmitted infections (STIs), has a long history, dating back to Surgeon General Thomas Parran, who, in 1937, proposed the establishment of formal surveillance systems for STIs. Because the prevention and treatment of STIs is covered in much greater detail elsewhere (see the excellent reviews by Low et al[55] and Stoner[56]), we focus here on the most salient points relevant to prevention.

Primary prevention involves measures taken to reduce the primary acquisition of STIs and to restrict the spread of infection when it occurs. These approaches include public health policies, such as educational programs that promote safe sex, consistent condom use, delaying first sexual contacts, and partner notification. Human

papillomavirus (HPV) is the first STI for which effective vaccines have been developed. A quadrivalent vaccine targeting cancer-causing and wart-causing HPV types is marketed under the name Gardasil, and a bivalent vaccine targeting only the cancer-causing HPV types has also been developed. Gardasil represents a potential prototypical preventive agent in the treatment of other long-term consequences of an STI, given that it is being promoted to children as early as age 9, before the initiation of sexual contact. In this respect, consideration of the implementation of a widespread vaccination program with Gardasil may be instructive for the prevention of other later-onset disorders, including schizophrenia. In the case of Gardasil, governments and public health organizations may need to contend with the perception that it may condone or even promote early sexual activity.[55,57]

Secondary prevention includes antibiotic treatment to individuals who have been exposed to an STI but who show no signs of infection. Several STIs are curable with antimicrobial therapy and include (but are not limited to) gonorrhea, chlamydia, and trichomoniasis. Gonorrhea was long treatable with many older antibiotics including penicillin and fluoroquinolone, but over time, it has acquired antibiotic resistance, leading to cephalosporin antibiotics as the drugs of choice.[58] Chlamydia, which resembles gonorrhea in its clinical manifestations, is treatable often with single-dose azithromycin or with tetracycline or fluoroquinolone antibiotics.[56] Trichomoniasis is cured with metronidazole or tinidazole.

Tertiary prevention involves treatment of individuals with incident STI in order to prevent others from acquiring the infection. These treatments include the antimicrobials described above. In addition, genital herpes, most commonly caused by HSV-2, can be treated with oral acyclovir, which reduces duration of clinical lesions and viral shedding in primary and recurrent infection.

Several strategies have been initiated at the programmatic level in order to implement these approaches. These include passive and active surveillance programs.[55] In passive surveillance, health authorities track case reports by clinicians and laboratory-testing facilities, which direct these authorities to changing epidemiological patterns. Active surveillance involves the use of screening or directed testing of large portions of the population in order to identify asymptomatic or subclinical infection. The particular method selected is generally predicated on the type of infection, the available resources, and the setting in which the infection occurs (ie, developed versus developing country).

Conclusions

It has been suggested that the overall decline in bacterial illnesses due to antibiotic therapy and the initiation of immunization programs may be at least partially responsible for the reduction in the incidence of schizophrenia in certain countries in the last several decades.[59] These and other preventive approaches are practical, relatively inexpensive, and often effective. One significant challenge will be the implementation of these approaches in resource poor countries, given that organizing large screening, treatment, and vaccination programs requires substantial amounts of funding. Nonetheless, if the associations between maternal infection and schizophrenia are replicated, it is our view that these preventive approaches may offer promise for the reduction in incidence of this disorder in the global population.

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