

## ⇒ Review Article



# Gestational Viral Infection and the Development of Neuropsychiatric Diseases in Offspring: A Possible Long-lasting Effect of COVID-19

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## Abstract

Coronavirus disease 2019 (COVID-19) continues to spread rapidly worldwide with significant infection rates and the risk for the development of psychosis. Currently, most studies have focused on the clinical and epidemiological features of inpatients suffering from COVID-19. However, less attention has been given to the long-lasting consequences of this infectious disease. Strong epidemiological studies mainly from the past influenza pandemics suggest the positive association between prenatal infection and increased incidence of schizophrenia in the offspring. Therefore, it can be postulated that prenatal exposure to COVID-19 virus may put the offspring at risk for the development of schizophrenia. For this reason, longitudinal studies of this population may help elucidate the pathomechanisms involved in this complex illness and provide an opportunity for reducing the impact of this disorder on the next generation. In this review, we discussed the evidence for the association between in utero exposure to infection and schizophrenia risk in the offspring.

**Keywords:** SARS-CoV-2 virus, Prenatal viral infection, Schizophrenia

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Received January 5, 2021, Accepted: February 3, 2021, Published Online: December 29, 2021

## Background

As a highly lethal pneumonia, coronavirus disease 2019 (COVID-19) continues to spread rapidly with approximately 84 million cases worldwide. Respiratory symptomatology such as cough, fever, shortness of breath, and fatigue has been reported to be the most frequent manifestations of COVID-19. However, growing evidence demonstrates that COVID-19 is also associated with neurological complications, which can range from anosmia as an early symptom and encephalopathy as the most common neurological feature in admitted patients (1). Interestingly, nearly 10%-35% of the people who survive COVID-19 infection have persistent neurological manifestations (2). Currently, most studies have focused on the clinical and epidemiological features of inpatients suffering from COVID-19 (3,4). However, less attention has been given to the long-lasting consequences of this infectious disease.

Strong epidemiological research has suggested the early-life complications, including pre- and early postnatal period as an important risk factor associated with the pathogenesis of neuropsychiatric disorders (5-

8). Specifically, infections during embryogenesis such as prenatal infection have been shown to cause deleterious effects on fetal brain development and consequently lead to the manifestations of neurodevelopmental diseases later in life (9,10). Consistently, a cohort study showed the increased incidence of schizophrenia in neonates born to mothers with clinical rubella (11). Added to this, maternal infection with various infectious agents such as influenza virus (5, 12) and *Toxoplasma gondii* (13, 14) have been also reported to increase the risk of schizophrenia in offspring. There is evidence that disruption in the immune balance between maternal and fetal environments, as a consequence of maternal immune activation (MIA), leads to disturbance in the normal brain development and finally increases the susceptibility of the offspring to develop neuropsychiatric diseases later in life. This possibility is strengthened by the epidemiological evidence confirming a link between MIA and neurodevelopmental diseases such as autism and schizophrenia (9, 15-17). The examination of post-mortem brains of individuals clinically diagnosed with mental disorders further supported the long-lasting

effect of MIA on offspring brain function and structure (18, 19). This evidence suggests that maternal infection with the novel coronavirus might also put the offspring at the risk for the development of neuropsychiatric diseases later in life. Therefore, it is of interest to suggest the monitoring and examinations of this population for associative relationships between prenatal infections and the development of neuropsychiatric disorders.

In the current review, we discuss the history of the previous viral pandemic to highlight the effect of prenatal viral infection on the pathogenesis of schizophrenia, as a possible long-lasting impact of COVID-19.

### Schizophrenia

As a severe psychiatric disease, schizophrenia affects nearly 1% of the global population, with usual onset in late adolescence or early adulthood (20). Schizophrenia has a broad phenotype, which is classified into positive symptoms, characterized by the existence of abnormal behavior, and negative symptoms, reflecting the absence of normal functions, and cognitive symptoms. This mental disorder severely affected behavior, cognition, and thought and significantly impair the social functioning of patients (21). Currently, the available treatments for schizophrenia are mainly effective for the management of positive symptoms with limited treatment options for both negative and cognitive manifestations (22).

With the unclear exact molecular mechanisms, schizophrenia is defined as a complex disorder, which results from an interplay of environmental and genetic factors. In this regard, different environmental risk factors for schizophrenia have been documented such as season of birth, vitamin D deficiency, immigration, birth complications, and drug abused. Of environmental factors, prenatal infection has been demonstrated to be a critical risk factor in the development of schizophrenia in the offspring. Both epidemiological and animal studies have exceedingly reported a link between MIA and neurodevelopmental disorders, including schizophrenia and autism in the adult progeny (23). In light of epidemiological findings, MIA in the animal model has been established upon injection of immunogenic substances to the pregnant female, which will be discussed in the next section.

### Influenza

As an infectious disease, influenza is caused by a virus, which predominantly attacks the respiratory system. The influenza virus particles are generally spherical with single-stranded RNA as a genome. There are four types of influenza virus, including A, B, C, and D. So far, influenza A viruses, with different serotypes, have been responsible for all influenza pandemics, for instance, H1N1 caused both Spanish flu in 1918 and Swine flu in 2009. As such, H2N2 and H3N2 caused Asian flu in 1957 and Hong

Kong flu in 1968, respectively (24).

Influenza usually causes a mild illness with common symptoms, including fever, sore throat, cough, muscle ache, and severe headache. In severe illness, however, influenza can cause critical complications with a potential for significant morbidity. As of today, numerous studies are reporting the acute and chronic neuropsychiatric manifestations of influenza (25). Based on these findings, the viral hypothesis of influenza has been suggested for many neuropsychiatric diseases including schizophrenia. With this background, some of the studies have mainly focused on the direct role of viruses in causing the disease, while others have focused on maternal infection during pregnancy as a causative factor for the development of schizophrenia in adult offspring. During the H2N8 pandemic of 1889–1892, neurological and psychiatric symptoms such as depression and insomnia were reported in infected patients (26). Similarly, Menninger was the first who reported the incidence of psychosis in patients of the 1918-1920 influenza pandemic (27). Interestingly, most of the early reports regarding the role of maternal viral infection in increasing the risk of schizophrenia in offspring have been based on data from the influenza pandemic with controversial results (6, 27, 28). While some of these studies demonstrated the positive link between maternal exposure to influenza and the development of schizophrenia in adult offspring (29-31), other reports were unable to confirm these results (32-34). The major drawback of these studies is the lack of reliable documentation about maternal influenza for which all the pregnant women during the pandemic were considered infected with influenza. Therefore, the results of these studies should be interpreted with caution. To counter this problem, more recent studies have used objective measures to determine maternal infection during pregnancy at the individual level (25). For example, in a population-based birth cohort study, Brown and colleagues measured influenza antibodies in maternal serum rather than the assumption of infection in pregnant women during the 1957 pandemic. They found a sevenfold increased risk of schizophrenia among the children of women who were infected with the influenza virus during the first trimester of pregnancy. Threefold increased risk was also reported for viral exposure in early-to-mid pregnancy with no significant results for exposure during late pregnancy (5). By contrast, another study that used the data from infected pregnant women showed no increase in the risk of schizophrenia in offspring (35). The hypothesis that infection during pregnancy may result in schizophrenia in offspring was strengthened by many epidemiological studies that reported the positive association between birth season (winter months) and increased risk of schizophrenia (36). It is worthwhile to note that maternal infection with other viruses such as rubella, herpes simplex virus (HSV), and *T. gondii* has

also been reported to be linked with schizophrenia risk later in life. This matter, however, is beyond the scope of this article and dealt with elsewhere (37).

Although these studies provide support for the critical role of maternal infection as a risk factor for developing psychiatric diseases in offspring, no conclusive evidence has been demonstrated for the influenza etiology of schizophrenia. Further studies are needed to address this issue in this pandemic which might be helpful to elucidate neurodevelopmental mechanisms involved in neuropsychiatric disorders.

### Rubella

In addition to the influenza virus, maternal infection with Rubella has also been suggested to be associated with the risk of psychotic disorders in the offspring (Table 1) (11, 38). The pathogenic agent of Rubella disease, Rubella virus, has been shown to have a neuroinvasive capacity which can directly interfere with fetal neurodevelopment (39). In support of this, a previous study on the 1964 Rubella epidemic reported the phenotype of autism spectrum disorder in 18 out of 243 offspring with congenital Rubella (40). This is further evidenced by another study on this epidemic which reported that 20% of the participants who were prenatally exposed to Rubella were diagnosed with schizophrenia spectrum disorder later in life (11).

### *Toxoplasma gondii*

As a pathogen, *T. gondii* has also been demonstrated to

increase the incidence of neurodevelopmental diseases in offspring (Table 1). In this regard, two cohort studies have reported the association between elevated levels of IgG antibodies to *T. gondii* in maternal sera and the increased risk of schizophrenia spectrum disorder in adult offspring. In the Parental Determinant of Schizophrenia (PDS) cohort study, Brown and colleagues reported an approximately twofold increase in the risk of schizophrenia in children who were born to mothers with high IgG antibody titer in late pregnancy (41). A similar trend was also observed in another cohort study in which the researchers demonstrated a link between increased maternal IgG to antibody against *T. gondii* and the elevated risk of schizophrenia in the offspring (42).

### Herpes Simplex Virus

There are two types of HSV, HSV-1 and HSV-2, which both cause viral infection in most humans. Several epidemiological studies have investigated the link between prenatal exposure to HSV and the risk of schizophrenia in adult offspring with conflicting results (Table 1). In some studies, in utero exposure to HSV-2 infection was found to be significantly associated with the increased risk of psychosis in adult offspring (15, 43). In line with this finding, another study also reported a 50% increased risk for the development of adult schizophrenia in offspring prenatally exposed to HSV-2 (44). However, other reports demonstrated no association between the risk of schizophrenia and prenatal exposure to both HSV-1 and

**Table 1.** Human Studies Demonstrating the Role of Prenatal Infection in Schizophrenia

Exposure Pathogen	Effect of Pathogen Infection on the Risk of Schizophrenia	Study Design	Reference
Influenza virus	↑	Ecological study	(12)
Influenza virus	↑	Ecological study	
Influenza virus	↑	Ecological study	(29)
Influenza virus	↔	Ecological study	(34)
Influenza virus	↔	Ecological study	(33)
Influenza virus	↑	Ecological study	(31)
Influenza virus	↔	Cohort study	(35)
Influenza virus	↑	Ecological study	(30)
Influenza virus	↑	Nested case control study	(5)
Influenza virus	↔	Ecological study	(32)
Rubella virus	↑	Cohort study	(11)
Rubella virus	↑	Cohort study	
<i>T. gondii</i>	↑	Nested case control study	(41)
<i>T. gondii</i>	↑	Case control study	(13)
HSV-2	↑	Nested case control study	(43)
HSV-2	↔	Nested case control study	(45)
HSV-2 and HSV-1	↔	Nested case control study	(42)
HSV-2	↑	Nested case control study	(15)
HSV-2	↑	Nested case control study	(44)

↑ Significant increase

↔ No significant difference

HSV-2 (13, 45). This discrepancy might be attributed to the methodological difference in studies and more epidemiological research is needed to address this issue.

### MIA Animal Models

A significant number of epidemiological studies have demonstrated the role of gestational infection in the etiology of neuropsychiatric disorders, which led to the neurodevelopmental theory of schizophrenia (13, 16, 19, 21). Based on this theory, pathological disruption of normal brain development may result in defective neural connectivity and cognitive dysfunction later in life. Indeed, studies on large population samples are considered an effective tool for investigating the relationship between prenatal infection and the risk of mental illnesses. Nevertheless, the establishment and use of animal models are beneficial for understanding the pathomechanisms involved in these debilitating mental disorders. For this reason, specific animal models of MIA based on the injection of infectious agents to pregnant females have been developed. In this regard, a few studies used prenatal viral infection with human influenza (H1N1) at various doses and time points to examine behavior, brain pathology, and genetic abnormalities of resulting offspring (46-49). Although the influenza model of MIA was similar to the human situation, it was associated with several limitations. Importantly, the use of live pathogens requires increased preventive safety measures to protect laboratory studies. Therefore, the administration of immunogenic substances such as bacterial lipopolysaccharide (LPS) and viral mimetic polyinosinic: polycytidylic acid Poly(I:C) to the pregnant animal has been extensively used as a valuable experimental approach to examine the underlying pathophysiological mechanisms of schizophrenia (17). As of today, many MIA animal studies have reported findings similar to patients with schizophrenia in offspring prenatally exposed to LPS or Poly(I:C), including structural abnormalities, behavioral impairments, increased level of inflammatory markers in the brain, CSF, and serum, and glial activations (17, 50-52).

Therefore, the use of MIA animal model, as well as epidemiological studies, is a suitable tool to elucidate the unclear viral etiology of schizophrenia.

### Mechanisms of Prenatal Infection Effects

The mechanism by which maternal infection induces delayed impairments in neural function and contributes to the manifestation of neuropsychiatric disorders such as schizophrenia later in life may include direct impact on fetal brain development and induction of cytokine/inflammatory response in both mother and fetus.

Several kinds of literature have suggested that neurodevelopmental alteration in offspring prenatally exposed to infectious agents including influenza virus,

HSV, *T. gondii* can be related to the direct impact of these agents on the fetal brain and placenta (39). This notion was supported by evidence from both cohort studies, as mentioned previously, and animal model studies. Using an experimental mouse model, two studies showed the persistence of viral RNA in the brain of pups prenatally infected with different serotypes of influenza viruses (53, 54). Added to this, another animal study showed alterations in placental structure with no evidence for the presence of viral RNA in both the placenta and fetal brain of offspring prenatally exposed to H1N1 influenza virus (55). This finding leads to the assumption that maternal cytokine response to the infectious agents might be involved in the pathogenesis of neuropsychiatric disorders in offspring.

The deleterious effect of prenatal infection on fetal brain development might be mediated by maternal immune response rather than a specific pathogen. In support of this several cohort studies have suggested the important role of inflammatory cytokines to mediate increased incidence of neuropsychiatric disorders in offspring prenatally exposed to infection (56, 57). Similarly, MIA animal studies based upon administration of different immunogenic agents including virus, synthetic viral mimic, bacterial endotoxin, and IL-6 have also confirmed the association between elevated levels of fetal and maternal cytokines and the development of phenotype related to schizophrenia in offspring (17). Added to this, animal studies have shown that prenatal exposure to immunogenic substances has also been linked with altered brain function and structure as well as neurobehavioral impairments in adult offspring (51).

### Conclusion

Since the 1918-1919 influenza pandemic, strong epidemiological and experimental studies have suggested prenatal viral infection as a critical risk factor for the development of neuropsychiatric diseases, which led to the viral hypothesis of schizophrenia. However, the mechanisms by which in utero infection interfere with the neurodevelopment of offspring and increase the risk of schizophrenia later in life are largely unclear. In this regard, recent findings suggest that MIA with increased levels of pro-inflammatory markers compromise the integrity of the placenta barrier and consequently leads to structural and developmental disturbance of the fetal brain. Concerning the evidence from historical influenza pandemics, it is possible that prenatal exposure to COVID-19 virus puts the offspring at risk for schizophrenia. Therefore, longitudinal studies of this population may help elucidate the pathomechanisms involved in this complex illness and provide an opportunity for reducing the impact of this disorder on the next generation.

### Conflict of Interests

None.



**Funding**

None.

**Acknowledgment**

The authors greatly acknowledge the clinicians and healthcare staff at Hormozgan University of Medical Sciences for their hard work and endless hours with patients diagnosed with COVID-19.

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