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Maternal immune activation virus related and schizophrenia

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Summary

Maternal immune activation (MIA) refers to the activation of the mother's immune system during pregnancy, which can have implications for the developing fetus. There is evidence suggesting that maternal immune activation, particularly due to viral infections during pregnancy, may increase the risk of certain neurodevelopmental disorders such as schizophrenia in the offspring. Research in this area has shown that exposure to certain viruses during pregnancy, such as herpes simplex, Zika, and influenza virus may contribute to alterations in fetal brain development, potentially leading to an increased risk of schizophrenia later in life. The exact mechanisms through which this occurs are still being investigated, but it's believed that the maternal immune response to the viral infection, including the release of inflammatory molecules called cytokines, may play a role in disrupting normal brain development. In this review of the literature on MIA and schizophrenia we will describe the potential implications of the findings from animal studies, epidemiological investigations, and clinical research to provide a preliminary understanding of this relationship.

Keywords: *Maternal Immune Activation, Schizophrenia, Neuroinflammation, Herpes Virus, Flavivirus, Orthomixovirus.*

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INTRODUCTION

Thought, perception, cognition, behavior and social cognition are all affected by the schizophrenia. Symptoms often appear during the latter stages of adolescence or early adulthood.

Although the exact cause of schizophrenia is not fully understood, it is believed to involve a combination of genetic, environmental, and neurobiological factors. Maternal immune activation (MIA) during pregnancy has received attention recently due to a theory that suggests immune response or infection in the mother can affect fetal brain development, increasing the risk of schizophrenia and other neurodevelopmental disorders in the offspring (Talukdar et al., 2020; Aguilar-Valles et al., 2020; Lins, 2021; Rubesa et al.,2018).

MIA refers to the exposure or infection of a pregnant woman with various immunogens, such as viruses, bacteria, and parasites. This may occur when the immune system is directly invaded by a virus, bacterium, or parasite, or when it is triggered by immune-related cytokines and chemokines, viruses or bacteria that mimic bacteria, or other environmental factors that are known to activate the immune system (Hall et al. 2023).

Torrey and Peterson proposed in 1972 that schizophrenia might potentially be attributed to a viral infection. The authors hypothesized that some types of schizophrenia may be associated with viral infection(Torrey & Peterson, 1976).

Research has shown that the prevalence of schizophrenia tends to reach its highest point during the winter and spring seasons, which aligns with the peak occurrence of certain viral infections.

Viruses may stimulate immunological reactions that can impact the development of the brain and raise the likelihood of schizophrenia in vulnerable individuals (Demler 2011; Schwartz 2011). In a recent study, Imamura et al. (2020) postulated that environmental factors, including prenatal exposure to infections, might potentially contribute to the development of the schizophrenia(Imamura et al. 2020).

Choudhury & Lennox (2021) found that maternal viral diseases, during pregnancy, increased the likelihood of developing schizophrenia(Choudhury & Lennox, 2021). However, according to Mote & Fulford (2020), not all ecological studies have been able to replicate these connections due to the potential impact of measuring the exposed population on the findings (Mote & Fulford, 2020).

The theory behind MIA is that when the mother's immune system is activated, either by infection, inflammation, or other factors, it can lead to changes in the developing fetal brain(Rubesa et al.,2018). This activation triggers the release of cytokines and chemokines that can

affect neurodevelopment, potentially increasing the risk of psychiatric disorders later in life(Chen et al., 2024b).

Due to the difficulty of conclusively correlating schizophrenia with viral infections occurring during pregnancy, few studies have investigated this relationship. However, despite the scarcity of evidence, it would be worth investigating whether certain viruses can affect the embryonic development of the central nervous system. This review investigated the occurrence of MIA during pregnancy resulting from viral infections, which has been associated with an increased risk of developing schizophrenia.

METHODS

A comprehensive literature review was performed using the SCOPUS and MEDLINE databases, covering publications from June 2023 to February 2024. Specifically, the following Boolean search string was applied: *(schizophrenia OR psychosis) AND (herpesvirus OR cytomegalovirus OR flavivirus OR orthomyxovirus OR coronavirus).* No restrictions were imposed on study design at the search stage. Retrieved records were screened for eligibility based on predefined inclusion and exclusion criteria.

RESULTS

Herpes Virus

Herpes Simplex Virus (HSV) infects humans, resulting in a variety of disorders ranging from mild simple oral or genital mucocutaneous infection to severe, life-threatening conditions, such as encephalitis (Whitley & Roizman, 2001; Xu et al., 2019).

HSV-1 infection can cause placental inflammation and hinder its proper functioning. Inflammation can impede the exchange of nutrients and oxygen between the mother and fetus, thus impeding fetal development. HSV-1 particles can infiltrate the central nervous system (CNS) by advancing down the axons and leaving from the outermost segment of the neurons (Kim et al., 2003).

Massrali et al. (2022) have shown that epidemiological investigations indicate a correlation between MIA and an increased susceptibility to schizophrenia caused by viral agents like HSV-1(Massarali et al. 2022). The association between HSV-1 and schizophrenia arises from its capacity to reproduce within the brain and its attraction to neurons. Furthermore, the findings imply that the presence of HSV-1 antibodies in children is linked to reduced cognitive function, indicating that exposure to HSV-1 during pregnancy may negatively impact neurodevelopment and cognitive ability in persons who have tested positive for the virus (Wang et al.,2019).

A potential rationale is that infection with HSV, especially during the development of the fetus or in early infancy, can cause inflammation and stimulate the expression of pro-inflammatory cytokines and chemokines. As a result, this might potentially cause changes in brain development and raise the likelihood of developing mental disorders, such as schizophrenia. Increasing data suggests that 'mild' HSV-1 brain infections might lead to neuronal damage like that seen in neurodegenerative diseases. (De Chiara et al., 2012; Marcocci et al.,2020)

Once a pregnant woman acquires HSV-1, her immune system responds to the virus by producing inflammatory cytokines such as IL-1 and IL-6, as well as immune cells that may cross the placenta and affect the development of the offspring. Toll-like receptors (TLR) may provide understanding of how HSV-1 infection triggers the activation of brain microglia and the inflammasome complex, which initiates inflammation. Microglia and astrocytes express TLR2, TLR3, TLR9, which can detect the presence of the HSV-1. Upon TLR activation, various inflammatory cytokines and chemokines linked to schizophrenia, including IL-1, IL-6, TNF-α, CXCL1, and CXCL2, are generated (Kotsiri et al., 2023;Wang et al., 2019; Paludan et al., 2011).

Animal studies have provided data that supports the association between MIA, HSV-1 infection during pregnancy, and the development of schizophrenia-like behavioral and neurological abnormalities in the offspring. These investigations frequently include exposing pregnant animals to immune stimulants or infectious agents, such as HSV-1, and assessing the impact on their progeny (Cheslack-Postava et al., 2015).

Other studies found that persons born to mothers who were exposed to HSV-2 during pregnancy have an increased probability of having psychoses in adulthood (Brown & Patterson, 2011; Khandaker & Dantzer, 2016; Buka et al., 2008).

A meta-analysis of twenty-three observational studies showed a statistically significant association between prior infection during pregnancy and the likelihood of children having psychosis(Zhou et al. 2019). Offspring of mothers who are exposed to HSV-2 have an increased risk of developing psychoses in maturity.

Cytomegalovirus (CMV) is a member of the herpesvirus family, specifically the Betaherpesviridae subfamily. It is an omnipresent virus that infects a significant fraction of the global population. CMV is spread mainly by direct contact with body fluids, including saliva, urine, blood,

and breast milk, from an infected individual. Transmission can also be facilitated by sexual intercourse, the donation of organs, the transfusion of blood, and from a mother to her fetus during pregnancy. In healthy people, CMV infection typically does not show symptoms or causes mild symptoms like the flu(Boeckh & Geballe, 2011).

Nevertheless, the virus has developed many strategies to avoid detection by the host immune system, enabling it to establish a long-lasting infection and experience intermittent reactivation(Cheeran et al.,2009). CMV has a 30–40% vertical transmission risk, and first-trimester infection predicts sensorineural loss and cognitive issues such as schizophrenia in neonates (Adler 2011).

CMV can traverse the placental barrier, a physical barrier that divides the circulatory systems of the mother and the growing fetus. This enables the virus to enter the fetus and potentially cause harm throughout its development. This may happen in many ways, such as direct infection of placental cells, transcytosis across placental endothelium cells, or by infected maternal immune cells that cross the placenta. CMV has the potential to alter the blood-brain barrier (BBB) of the growing fetus and cause permanent damage to its structure. The malfunctioning BBB has been associated with schizophrenia(Kealy et al. 2020). CMV, which remains dormant in fetuses, may become active after birth and reduce the permeability of the BBB by stimulating microglia and triggering an inflammatory reaction. CMV's affinity for the nervous system may result in various neurological problems, including microcephaly, periventricular calcifications, white matter abnormalities, and neuronal migration disorders (Ganguli & Chavali, 2021, Mohebalizadeh et al., 2023, Elgueta et al.,2022).

Flavivirus

Flaviviridae family includes Dengue, Zika (ZKV), Japanese encephalitis, and West Nile Virus (WNV)(Pierson et al. 2020).Arthropod vectors, such as mosquitoes and ticks, mostly transmit these viruses. Nevertheless, some viruses can also be transmitted vertically from mother to fetus during pregnancy or through blood transfusion.

Flaviviruses possess a genome that is composed of a single-stranded, positive-sense RNA. This organism's genetic material consists of a single polyprotein split into many structural and non-structural proteins throughout the viral replication process. Flaviviruses have three types of (Zhao et al.,2021)structural proteins: the capsid protein (C), the membrane protein (prM/M), and the envelope protein (E). Flaviviruses may elicit diverse clinical symptoms in individuals, spanning from asymptomatic infection to severe and sometimes lethal infection. (Zhao et al. 2021)

Once viruses have effectively crossed the placental barrier, they may bypass fetal brain barriers via several paths(Ayala-Nunez et al. 2019). Many authors found that neurotropic viruses like WNV and ZKV compromise the strength of BBB and placental barrier by reducing the presence of tight junction proteins through the production of pro-inflammatory cytokines such as TNFα (Kaur et al., 2023;Mustafá et al., 2019a; Marshall et al.,2022; de Vries & Harding, 2023). Moreover, ZKV can enter the BBB by transcytotic or paracellular pathways without causing any harm to the integrity of the membrane(Mustafá et al. 2019b). The virus infiltrates peripheral lymphocytes or monocytes, which can penetrate the brain through paracellular or transcellular pathways, breaking the BBB.

ZKV infection during pregnancy has been linked to a range of neurodevelopmental problems in neonates, including microcephaly, brain deformities, and developmental delays. Although schizophrenia is classified as a neurodevelopmental condition, it usually becomes apparent throughout adolescence or early adulthood. This makes it difficult to establish a clear connection between ZKV infection during pregnancy and the development of schizophrenia (Joob & Wiwanitkit, 2020; Pierson et al.,2020).

Orthomyxovirus

Orthomyxoviridae is a group of RNA viruses that includes Influenzavirus (IV). Influenza virus subtypes are distinguished by the specific combinations of surface hemagglutinin (H) and neuraminidase (N) proteins they possess. Viruses linked to seasonal influenza outbreaks in humans often include subtypes like H1N1 and H3N2(Russell 2008). IV during pregnancy could play a deleterious effect on the health of both the mother and the fetus, but the exact biochemical pathways behind this phenomenon are not fully understood(Oseghale et al. 2022).

Hyperthermia causes harm to the developing amygdala-hippocampal complex and related structures in the embryonic brain. This may help us understand why there is a connection between maternal influenza and other sources of fever during the second trimester and the development of schizophrenia in adulthood (Edwards 2007).

Following considerable early organ development, exposure to high temperatures can cause anomalies in the central nervous system and other organs. Neuroblasts that are activated undergo cell death, leading to cell migration and arborization disruption. Additionally, vascular damage ensues(Edwards 2007).

During pregnancy, the influenza virus affects the brain system development of monkeys in animal models. It results in a decline in gray matter in most regions in the

cortex and a decrease in white matter, particularly in the parietal cortex. This might heighten the likelihood of acquiring behavioral problems(Short et al. 2010).

Moreover, the H1N1 virus is strongly attracted to dopaminergic neurons under controlled conditions. This attraction induces the activation of the nuclear factor kappa B (NFkB), a transcription factor linked to inflammation, resulting in cellular apoptosis. Infants born to mothers who are infected with the same strains of the virus during pregnancy suffer from a reduction in dopaminergic neurons and have abnormal behaviors(Landreau et al. 2012).

In animal studies, the offspring of moms infected with the influenza virus have an increased abundance of the 5-HT(2A) receptor and a reduction in the mGlu(2) receptor in their frontal cortex. This mutation might potentially be a contributing factor to the observed alterations in neurotransmission that are linked to schizophrenia(Moreno et al. 2011).

Conversely, the A(H1N1) vaccine injection protected the children against cognitive impairment produced by LPS. The results suggest that providing the influenza vaccination to pregnant moms promotes the development of new neurons and boosts the behavioral ability of their offspring. In addition, it offers protection against the detrimental effects induced by LPS throughout the offspring's development (Xia et al.,2014).

DISCUSSION

The MIA hypothesis proposes a link between maternal immune activity during pregnancy and an increased probability of children having schizophrenia and other neurodevelopmental disorders(Cieślik et al. 2020). This notion suggests that when a mother has an infection or an immune reaction during pregnancy, it may lead to altered development of the fetal brain, ultimately increasing the vulnerability to schizophrenia(Bergdolt & Dunaevsky, 2019).

Guma et al. (2021) proposed that MIA acts as a disease primer, making people more susceptible to genetic alterations and environmental influences that might lead to the development of symptoms associated with illness in the future (Figure 1). It is essential to identify the specific risk factors that contribute to maternal infections and understand how they interact with each other in order to get a comprehensive understanding of the underlying mechanisms and develop effective treatments(Bosserez et al., 2023;Guma et al.,2021).

When transmitted to a pregnant woman, HSV, CMV, ZKV, and IV may impact the development of the offspring's brain via infection-related pathways. As a result, the mother's body releases pro-inflammatory cytokines(Rubesa et al. 2018), which then trigger inflammation in the fetus's brain. Additionally, these viruses can directly infect neural cells in the fetus (Elgueta et al. 2022) (Figure 2).

To gain a deeper understanding of the basic underlying processes of schizophrenia and the impacts of MIA, Chamera et al. employed animal models, specifically those utilizing polyinosinic: polycytidylic acid (poly I: C), to induce MIA and simulate viral infections that take place during pregnancy(Chamera et al. 2021). Specifically, the timing of MIA during pregnancy impacts the observable traits shown by the offspring. In a study conducted by Druart et al. in 2021, mice were intentionally subjected to MIA during the first stages of pregnancy (gestational day 9). The ensuing offspring had traits that corresponded to the positive symptoms of schizophrenia (Druart et al., 2021). Nevertheless, when MIA was commenced during the early second trimester (specifically on gestational day

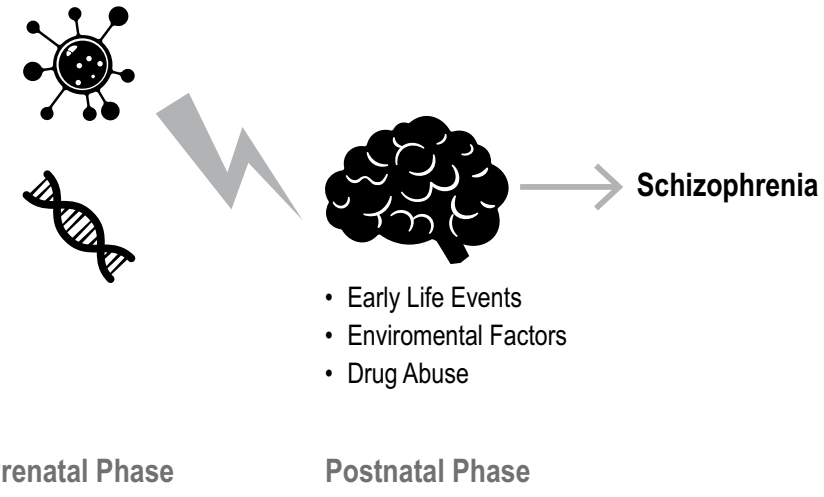


Figure 1. Etiological Factors of the Schizophrenia
Pre-natal factors such as DNA and viruses associated with post-natal factors biological (substance use), psychological, such as early life events (trauma, early losses, abuse), social (pollution, deprived urban contexts).

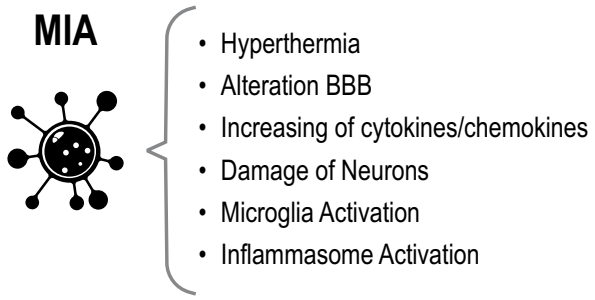


Figure 2. Features associated with Maternal Immune Activation (MIA)
MIA induces hyperthermia, disrupts brain blood barrier, increases pro-inflammatory cyto-chemokines, activates microglia and inflammasome. All these factors stimulate microglia.

17), the offspring exhibited traits that aligned with the adverse and cognitive symptoms often linked to schizophrenia(Druart et al. 2021).

Studies have shown that the timing of MIA during neurodevelopment significantly affects the distribution and mobility of neurons. This indicates that the precise timing of exposure to MIA is essential in determining the developmental alterations observed in neurons maturation and migration. The study also shown that animal models of MIA helped establish a connection between the disruption of the complement system, a crucial part of the immune system, and a higher likelihood of acquiring symptoms similar to schizophrenia (Talukdar et al. 2020).

Concerns have arisen about the potential effects of severe acute respiratory syndrome coronavirus two (SARS-CoV-2) on the neurodevelopment of babies born to mothers who were infected with the virus during the recent COVID-19 pandemic. A recent study suggests that respiratory syncytial virus infection may increase the likelihood of developing mental problems. Understanding the causes of developmental disorders improves efforts to prevent, diagnose, and treat these illnesses(P. M. Brown et al. 2017; Manti et al. 2024).

Viral infection can activate inflammatory pathways that generate various biomarkers and lead to tissue alterations, indicating the existence of chorioamnionitis (inflammation of the uterus) or funisitis (umbilical cord inflammation). Some evidence suggest that infections and inflammation experienced by the mother at important phases of fetal development might cause changes in the structure and function of the brain, which are depending on the timing of the exposure.

Mueller et al. found that when the mother's immune system is triggered by infection or inflammation, it releases different immune cells and molecules, such as pro-inflammatory cytokines, chemokines, and antibodies(Mueller et al., 2018; Mueller et al.,2020). These substances can pass through the placenta and impact fetal brain development.

Therefore, initiating immunological stimulation during the early stages of gestation can help sustain changes in microglia, which in turn can reconfigure brain networks. Postnatal behavioral disorders are linked to the process of rewiring the brain. An elevation in activated microglia is essential for combating pathogenic microorganisms, but prolonged activation leads to neurodevelopmental complications(Chen et al., 2024). Excessive synthesis of complement components by activated microglia can lead to abnormal synaptic pruning.

These alterations affect the growth and connectivity of the brain circuits responsible for cognitive functioning, emotional control, and sensory information processing. MIA may produce an imbalance in the neurotransmitter systems of the developing brain, notably involving dopamine, glutamate, and gamma-aminobutyric acid. This imbalance is associated with the development of schizophrenia(Winter et al., 2009; Hadar et al., 2015). Choudhury and Lennox found that research on animal and human imaging investigations indicates that MIA can lead to structural and functional brain problems(Choudhury & Lennox, 2021). Similarly, confirmed that these anomalies may encompass alterations in brain volume, cortical thickness, connection patterns, and atypical neural activity patterns, specifically in schizophrenia-related areas(Handunnetthi et al. 2021).

CONCLUSION

Converging epidemiological and experimental evidence implicates MIA, most frequently arising from viral infections during pregnancy, as a significant risk factor for schizophrenia in offspring. Preclinical models have been instrumental in delineating the temporal sensitivity of MIA exposure and in identifying candidate neurobiological mechanisms, including aberrant neuronal migration and complement system dysregulation. Importantly, MIA exposure does not confer deterministic risk, as only a subset of exposed individuals subsequently develop schizophrenia. This heterogeneity highlights the critical role of moderating factors, such as genetic vulnerability, the timing, magnitude, and chronicity of immune activation, and co-occurring environmental insults, in shaping disease trajectories and underscores the complex, multifactorial architecture of schizophrenia. A refined understanding of MIA-related neurodevelopmental perturbations carries

substantial implications for risk stratification, early detection, and the development of targeted preventive and therapeutic interventions. However, substantial gaps remain in elucidating the precise molecular, cellular, and circuit-level mechanisms through which MIA exerts long-term effects on brain development. Addressing these gaps will be essential for translating mechanistic insights into clinically actionable strategies.

Ethical considerations: the study does not include human subjects.

Conflict of interest: authors declare to have no conflict of interest. Hereby all authors disclose that they do not have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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Authors' contributions: AM contributed to the conception and design of the work; AM did the analysis of the data and conducted literature research; AM drafted the first version of the paper; MSS revised the paper critically; authors have approved the final version and agree to be accountable for all aspects of the work.

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