

# **Predicting the future of mental health: (how) will *in utero* COVID-19 infection influence psychiatric illness in future generations?**

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## **Abstract**

**Objectives:** There is limited research on the potential future psychiatric effects of *in utero* COVID-19 infection. There is evidence that COVID-19 infection can lead to adverse neonatal outcomes. Obstetric complications and neurodevelopmental insults such as viral infections have been implicated in the development of some mental disorders including schizophrenia (SZ). The aim was to address the possible mechanisms and influences related to *in utero* infection that could increase the risk of mental illness in the future.

**Methods:** Searches were conducted in the databases PubMed, Embase, and PsycINFO for studies involving COVID-19 infection and pregnancy, obstetric complications, and psychiatric complications. Search results were thoroughly evaluated to identify relevant literature sources. Reference sections of these sources were also assessed for potentially pertinent information. Additionally, any external information outside of these search terms was sourced from the databases mentioned.

**Results:** Three main components of *in utero* COVID-19 infection are discussed: obstetric complications, maternal infection, and fetal infection. All in all, infection-related processes that compromise oxygen delivery, augment inflammation in the mother or the fetus, or exacerbate psychological stress could impair proper neurodevelopment. Several studies found evidence of significantly higher preterm delivery and cesarean section rates associated with COVID-19 infection. Other noted adverse birth outcomes included fetal distress, stillbirth, low birth weight, neonatal asphyxia, and pre-eclampsia. Associated birth complications were found to be most severe and prevalent during the third trimester, a crucial neurodevelopmental period.

**Conclusion:** It is plausible that disruptions in brain development caused by *in utero* COVID-19 infection could increase the risk of mental illness development in the offspring. The observed implications of COVID-19 along with known neurodevelopmental complications of *in utero* infection provide multiple processes that could impact their future mental health. This increased risk could arise from neonatal outcomes associated with COVID-19 infection, the consequences of maternal infection on the fetus, or direct viral infection of the fetus and fetal brain. Due to its novel nature, more evidence is needed to determine the exact prevalence of adverse obstetric outcomes, vertical transmission, effects on neurodevelopment, and development of mental illness due to SARS-CoV-19 used to predict the risk.

**Keywords:** COVID-19; *in utero* infection; psychiatric disorder; mental illness; obstetric outcomes; obstetric complications; SARS-CoV-19; neurodevelopment

## Introduction

Due to the novel nature of COVID-19, there is limited understanding of the long-term effects of the disease in future generations. Research has linked viral infection with psychiatric disorder development later in life, particularly prenatal influenza infection to an increased risk of SZ. This phenomenon can be explained by the multi-hit hypothesis, which states that an initial insult (or “hit”) to an individual increases susceptibility to another insult that subsequently increases the risk of developing psychiatric disorders. Hits include genetic dispositions, adverse birth outcomes, maternal infection or stress, traumatic events, drug use, stress, etc. (Guerrin et al., 2021). Recent studies have associated COVID-19 with obstetric complications and adverse neonatal outcomes, which will be furthered explained in the next section. The present manuscript intends to explore the extent and ways that *in utero* COVID-19 infection can serve as a “hit,” or how associated mechanisms can disrupt neurodevelopmental processes and, thus, elevate the risk of psychiatric disorder development in the future.

## Obstetric Complications Associated with COVID-19 Infection

An increased occurrence of obstetric complications has been associated with maternal COVID-19 infection. According to a review done in November 2020, the most common difficulty seen is preterm delivery, which had a prevalence between 22.7% and 32.3% (Papapanou et al., 2021). This rate is high compared to the global preterm birth incidence of 11% (Walani, 2020). Other complications have been observed, such as fetal distress (8.5%), stillbirth (0.6%), low birth weight (8.7%), abnormal Apgar scores (2.2%), neonatal asphyxia (0.6%), and NICU admission (27.3%) (Papapanou et al., 2021). Thrombosis has been observed in fetal placenta, contributing to instances of cesarean section in infected patients (Soheili et al., 2021). It is important to note that research on this issue is still developing, and more evidence is needed to have a definitive interpretation of birth complications influenced by COVID-19 infection.

COVID-19 infection in the third trimester appears to be more severe than in the other trimesters. One *in utero* COVID-19 study showed that low birth weight, premature birth, and NICU admission seemed to be more common in the third trimester, with a rate of 10% (Soheili et al., 2021). A different cohort study demonstrated that infection during the first and second trimesters was not associated with adverse neonatal outcomes with a 100% perinatal survival rate and a healthy average birth weight (Rosen et al., 2021).

## **Linkage Between Obstetric Complications and Neurodevelopment**

### **Role of GM and WM in neurodevelopment**

The brain is composed of grey matter (GM) and white matter (WM); GM contains the somatic body, dendrites, and nonmyelinated axons of the neuron, while WM contains the myelinated axons of the neuron. GM contains the processing unit of the neuron, while WM is responsible for communication throughout the central nervous system (CNS) (Wen & Chklovskii, 2005). Abnormal changes in GM and WM are consistent with developmentally based psychopathologies, such as SZ and Bipolar Disorder (BD). WM and GM have been shown to differentiate in a stringent pattern (Moura et al., 2017), and any disruptions in this course can be assumed to affect interconnectivity and interpretation of information in the CNS.

The brain morphology of SZ exhibits enlarged ventricles, overall decreased volume, and reduced size of the hippocampus and thalamus. Structural MRIs demonstrate that there are alterations to the cortical volume, thickness, and folding patterns of the frontal and temporal lobes (Haukvik et al., 2013). Similarly, BD tends to have similar alterations to GM microstructure in the frontal and temporal lobes (Anderson et al., 2013). Comparing the morphology of SZ, BD, and major depressive disorder (MDD) indicates that major psychiatric disorders have similar abnormalities but differ in their specific regions. All three have decreases in GM volume, but the specific areas affected are distinct to each disorder. SZ and BD both demonstrate altered WM microstructure, while MDD does not (Chang et al., 2018). These morphological patterns serve as a predictor for future mental illness development.

Any perinatal process that can alter the model maturation pattern of the brain and decrease total brain volume should be considered to increase the risk of psychiatric disruptions in the future. Abnormalities that lead to decreased CT or GM microstructure alterations are signs of several major psychiatric disorders, while decreased FA, WM microstructure alterations, and enlarged ventricles signal increased risk of SZ or BD as well.

### **How abnormal birth outcomes attributed to COVID-19 can affect neurodevelopment**

The fetal brain develops exponentially during the third trimester in preparation for birth. As obstetric complications are most common during this period, it is important to address which processes are affected. Beginning this trimester introduces the presence of limbic and projection fiber bundle growth, meaning an increase in WM. Normally, the third trimester continues

development of these microstructures and reorganization due to differentiation events of the brain (Shadab et al., 2019). Furthermore, this period is crucial for the formation of synapses, neuronal migration, and myelination (Lammertink et al., 2021). The emergence of gyri and sulci, which compose the grooves and folds, respectively, of the brain, is known as gyrification; this essential process occurs during this period as well (White and Hilgetag, 2008).

One study found that decreased total brain volumes and changes to WM microstructure are likely to be the cause of adverse neurodevelopmental effects in moderate-late preterm infants (Kelly et al., 2020). These results demonstrate how interruptions to growth during late pregnancy, such as preterm birth, can impact fundamental morphological structures and lead to altered brain function. Pre-term delivery and low birthweight are two outcomes common to COVID-19 infection; both outcomes could limit the oxygen and blood supply necessary for cell survival and growth in the brain, and it is reasonable to expect that similar results to the study above could occur. These growth disruptions can have consequences on the connectivity, framework, and functionality of the brain, leading to WM disruptions consistent with major psychiatric disorders. Disturbance to gyrification may lead to the altered folding patterns are characteristic of SZ.

One obstetric complication seen with COVID-19, pre-eclampsia, a placental disease, can have long-lasting consequences on fetal neurodevelopment. Antiangiogenic protein sFLT1 has been associated with this disease (Rana et al., 2019), which could be significant due to similar use of the renin-angiotensin system and its structures in the pathophysiology of COVID-19. Loss of the protective ACE2 function due to COVID-19 infection can cause an increase in angiotensin, Ang II, and aldosterone, explaining the extremely inflammatory nature of pre-eclampsia. This condition is marked by hypertension and proteinuria in the mother (Dhaundiyal et al., 2021). Normally peak Ang 1-7 plasma levels have been shown to be lower during pre-eclampsia, which adds to loss of protective function (Todros et al., 2020). Although little is known about the pathophysiology of pre-eclampsia, the disorder's inflammatory nature is derived from a dysfunctional RAS, signifying that COVID-19 infection could be a predisposing factor.

Pre-eclampsia is a placenta-mediated disease and one complication, placental ischemia, where the placenta sticks to the uterine wall, causes intrauterine growth restriction (Gumusoglu et al., 2020). In fetal growth restriction, the fetus does not receive proper nutrients and oxygen, and GM is distinctly subject to transformations. WM maturation, myelination, synaptogenesis, and creation of complex neuronal networks are all processes that can be disrupted as well

(Dudkink et al., 2021). The lack of necessary resources to the uterus places the fetus at risk of deficit growth and morphology consistent with psychiatric disorders.

### **Possible Mechanisms of Psychiatric Complications due to Viral Infection**

#### **Maternal viral infection**

Maternal Immune Activation (MIA), the maternal immune response to infection, has been found to increase the risk of neuropsychiatric disorder development in offspring. MIA often works with another insult, such as stress or mutation, to lead to psychiatric disorder. It has been hypothesized that MIA affects the function of the maternal cytokines and the major histocompatibility complex I (MHCI), which are significant to fetal neurodevelopmental processes, especially synaptogenesis and formation of neural circuits (Estes and McAllister, 2016). Poly (I:C) is a viral agent that induces MIA through Toll-like receptor (TLR) pathways, namely TLR3 and TLR4 (Bergdolt and Dunaevsky, 2019). These same receptors are activated by SARS-CoV-2, often resulting in the inflammatory nature of COVID-19 infection; the consequence is a disequilibrium with an excess of cytokines IFN- $\gamma$ , TNF- $\alpha$ , IL-2, IL-4, IL-6, IL-8, IL-1 $\beta$ . (Manik and Singh, 2021). Excess IL-8 in the second half of gestation has been associated with decreased cortical volumes, and IL-6, and excess TNF- $\alpha$  in the third trimester have been associated with the impaired synaptic process. Microglia have been found to adopt abnormal functions due to prenatal overactivation of cytokines; these atypical microglia and cytokines are consistent with that found in SZ (Allswede and Cannon, 2018). These cytokines can pass through the fetal blood brain barrier, after it has developed in late gestation. Microglia have essential roles in neurodevelopment. In late gestation, these cells are responsible for proper synapse formation and synaptic pruning; however, abnormal activation of microglia may lead to disruptions in pruning (Prins et al., 2018). Epigenetic consequences associated with MIA, such as dysregulation of methylation and alterations to histones and microRNA, have been associated with impaired neuronal structure and synaptogenesis.

Loss of the protective, anti-inflammatory function of ACE2 due to COVID-19 infection leads to vasoconstriction, and decreased lung capacity can diminish oxygen levels, leading to insufficient transport of nutrients and oxygen to the fetus. Improper nourishment can compromise brain volume, and connectivity, similarly to the effects of placental ischemia. Similarly, maternal psychological stress caused by infection, can restrict placental blood supply (DeSocio, 2018), and

solicit a fetal stress response. By the third trimester, the fetal HPA axis has developed; thus, cortisol from the mother can pass through the placenta, and trigger stress response in the fetus. Normally, a protective enzyme, 11b-HSD2, converts cortisol to inactive cortisone to regulate the levels of cortisol that can reach the fetus. However, in response to increased psychological maternal stress, 11b-HSD2 can be desensitized, leading to higher levels of circulating cortisol in which the fetus is able to react. Fetal exposure to stress has been associated with epigenetic adaptations to cortisol, which can transfigure neural circuits and brain structures. For example, increased methylation of NR3C1, the gene for glucocorticoid receptors, suppresses the cortisol negative feedback loop in the hippocampus and can lead to higher cortisol levels in the offspring, and decreased methylation of the BDNF gene, which stimulates and accelerates neuronal development (DeSocio, 2018). Essentially, high cortisol levels can cause the developing fetal brain to be chronically stressed. The fetus' brain may "assess" this high stress environment as a message to enter a "survival mode" and speed up growth as necessary, hindering a proper and controlled neurodevelopment.

### **Fetal viral infection**

It is important to assess the potential consequences of direct fetal COVID-19 infection. One study showed that pregnant women have a higher expression of ACE2 in reproductive organs, uterus, and placenta. Additionally, there is evidence of fetal ACE2 expression in the heart, liver, and lung (Dhaundiyal et al., 2021). Thus, if COVID-19 can pass through the placenta and interact with fetal ACE2 receptors, there can be major developmental consequences on the organs mentioned; additionally, blockage of these receptors can impact organogenesis of the kidney, brain, lung and heart (Song et al., 2012). Improper development of these organs can limit oxygen and nutrient supply essential for proper neurodevelopmental growth.

Evidence of COVID-19 infection in brain tissue has been noted in autopsy reports, many of which displayed acute hypoxic injury, nonspecific inflammation, and hemorrhage (Mukerji and Solomon, 2021). If infection of the fetal brain is possible, it is important to consider how it would affect neurodevelopment. It can be predicted that lack of oxygen can cause growth deficits, and inflammation can have profound functional effects on microglia and inflammatory molecules, and thus, any processes associated with their regulation (e.g. synaptogenesis, synapse pruning, neuronal formation).

Furthermore, it is highly probable that both the central renin-angiotensin system (RAS) and local RAS in the brain are developed by late gestation, and that their components have significant roles in fetal development; angiotensinogen has been associated with brain maturation and neurogenesis, while angiotensin peptides in the local RAS, such as Ang I, Ang II, Ang III, and Ang (1-7) have been associated with cardiovascular and endocrine regulation (Mao et al., 2009). Thus, it can be assumed that the blocking of the ACE2 receptor can cause an imbalanced pro-inflammatory response in the fetus. In gestation, the overactivation of microglia and cytokines triggered by inflammation can compromise neuroimmune function and proper neurodevelopment due to unregulated neuronal apoptosis and formation. Increased IL-8 in the third trimester has been associated with enlarged ventricles and increased expression of CNS-specific immune molecules have been found postmortem in patients with SZ (Miller et al., 2012). Formation of Ang (1-7) would be blocked which can result in vasoconstriction and oxidative stress, and, therefore, long-term cardiovascular effects and insufficient delivery of nutrients and oxygen throughout the developing fetus. Damage to the brain can include loss of volume and surface area, reduced neuroplasticity, altered connections and overall abnormal neurodevelopment.

### **Pandemics and SZ: what can flu teach us about COVID-19?**

Due to the novelty of COVID-19, it is difficult to predict how seasonality will affect transmission; however, it is reasonable to make predictions in accordance with influenza, a similar viral respiratory illness that has been found to peak during winter. Environmental conditions, such as drier climates and lower temperatures, compromise innate and respiratory defense responses and promote respiratory illness transmission; these conditions explain why human coronaviruses tend to peak in the winter as well (Moriyama et al., 2020). The correlation between *in utero* influenza infection and increased risk of SZ has been substantially researched. An epidemiological study based on a large cohort in Spain found that there is a significant relationship between increased risk of SZ and birth during the winter to spring period of each of the years that the Spanish influenza pandemics occurred (Alvarez-Mon et al., 2021). It is reasonable to expect that winter may be a resurgent period for COVID-19 infection in the future. It can be anticipated that there will be a higher risk of COVID-19 related obstetric complications

and future psychiatric disorder development for winter births, as observed with previous pandemics.

### Conclusion

The pathophysiology of *in utero* COVID-19 infection was categorized into three distinctive categories (obstetric outcomes, maternal infection, and fetal infection), to determine how the specific disordered processes in each aspect could affect fetal neurodevelopment. After evaluation and synthesis of available literature, it is reasonable to predict that *in utero* COVID-19 infection could trigger mechanism detrimental to fetal neurodevelopment and heighten the risk of mental illness development in the future. Because infection tends to be most prevalent and severe during the third trimester, neurodevelopmental processes during that period were considered. A relationship was found between the potential brain morphology compromised due to infection and morphological patterns found in major psychiatric disorders.

Observed obstetric outcomes, such as preterm birth and preeclampsia, can potentially severely impact neurodevelopment due to the multisystem inflammatory nature of COVID-19. The inflammation, stress, and pathophysiology associated with maternal infection can compromise the health of the placenta, and thus, the developing fetal brain. Fetal infection can lead to abnormal brain development, in addition to impaired organogenesis of the lungs and heart. The observed implications of COVID-19 along with known neurodevelopmental complications of *in utero* infection provide multiple processes that lead to neurodevelopmental patterns characteristic to psychiatric disorders.

Because SARS-CoV-19 is a relatively novel disease, more evidence is needed to determine the exact prevalence of adverse obstetric outcomes, vertical transmission, and impaired neurodevelopment. As relevant literature becomes available on the subject, a more advanced analysis is necessary to determine the exact risk of mental illness development in future generations. It is important to recognize that COVID-19 itself will likely not be the single cause of psychiatric disorders, which require a precise interplay of genetic and environmental factors, such as stress, adverse events, etc. It is important to explore the role of viruses as a factor, as continuing to enhance understanding of the roots of psychiatric disorder development will facilitate prevention, diagnosis, and treatment advancement of these disorders.



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