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Mini-Narrative Review

Maternal COVID-19 infection and the fetus: Immunological and neurological perspectives

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ABSTRACT

Immunoneuropsychiatry is an emerging field about the interaction between the immune and nervous systems. Infection and infection-related inflammation (in addition to genetics and environmental factors) can act as the etiopathogenesis of neuropsychiatric disorders (NPDs). Exposure to COVID-19 in utero may be a risk factor for developing NPDs in offspring in the future. Maternal immune activation (MIA) and subsequent inflammation can affect fetal brain development. Inflammatory mediators, cytokines, and autoantibodies can pass through the placenta and the compromised blood-brain barrier after MIA, leading to neuroinflammation. Neuroinflammation also affects multiple neurobiological pathways; for example, it decreases the production of the neurotransmitter serotonin.

Fetal sex may affect the mother's immune response. Pregnant women with male fetuses have been reported to have decreased maternal and placental humoral responses. This suggests that in pregnancies with a male fetus, fewer antibodies may be transferred to the fetus and contribute to males' increased susceptibility/vulnerability to infectious diseases compared to female infants.

Here, we want to discuss maternal COVID-19 infection and its consequences for the fetus, particularly the neurological outcomes and the interaction between fetal sex and possible changes in maternal immune responses.

1. Introduction

Immunoneuropsychiatry is an emerging field related to neuropsychiatric disorders that has received much attention [1]. In this field, it is believed that immune disturbance contributes to the development neuropsychiatric disorders (NPDs) [1,2]. At the same time, the immune system is necessary for optimal brain functioning; its disruption/dysregulation leads to damage to the nervous system and neurological disorders [1]. In recent years, immune-based treatment has been emphasized as an adjuvant treatment for this range of diseases [1–3].

Certain viral infections in pregnant women lead to poor outcomes for the mother and fetus; for example, chickenpox is not severe in children, but chickenpox infections are serious in pregnant women and can lead to pneumonia and death. In addition, the mortality rate of pregnant women due to H1N1 influenza in 2009 was higher than the rate of the general population [4–10]. In the COVID-19 pandemic, pregnancy has been recognized as a risk factor for infection severity and mortality [11]. In one study, admission to an intensive care unit and mechanical ventilation in pregnant women with COVID-19 were five and four times higher than in non-pregnant women [12,13]. Additionally, an increase in adverse pregnancy outcomes, such as preterm birth in women with COVID-19 compared to uninfected pregnant women, has been reported [11,14,15]. The likelihood of their neonates being hospitalized is also three times higher, although several vaccines and traditional and modern treatment platforms have been developed and evaluated for COVID-19 [15–19]. While many studies have investigated neurological symptoms in adults with COVID-19, limited studies have yet been conducted on neurological morbidities in children exposed to COVID-19 in utero [20–22]. Previous pandemics have shown that in-utero exposure to some infectious agents (such as rubella and influenza) is a risk factor for increased future neurological outcomes in children born during pandemics. The 1964 rubella pandemic increased autism spectrum disorders and schizophrenia among children born during the pandemic [20,23].

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Also, neurological disorders have been reported in children born during the influenza pandemic [20]. Therefore, there may be a link between in-utero exposure to COVID-19 and future neurological disorders in offspring in later life, as early studies indicate this relationship.

A study on children born during the COVID-19 pandemic at six months showed that children born during the pandemic had lower scores on gross motor and personal-social than children born before the pandemic [20].

Another study was carried out on 7772 infants born during the COVID-19 pandemic. The results showed that the likelihood of diagnosing neurological disorders in infants born (at the age of one year) from mothers infected with COVID-19 is higher than in infants born to uninfected mothers [21]. In today's world, various aspects of infectious diseases, such as epidemics, especially with emerging and re-emerging agents, drug resistance and infection with organisms with lesser-known effects on human cells and bodies, have brought the most significant potential risks to humanity. In the meantime, their effects on pregnant women, their fetuses, and children are much more important [2,6,24–29].

These preliminary results show that in-utero exposure to COVID-19 may be associated with future NPDs. Therefore, children of infected mothers should be monitored after birth and in the future. According to this evidence, it is necessary to review the possible mechanisms of maternal COVID-19's effects on the nervous and immune systems of the fetus.

Here, we want to discuss maternal COVID-19 and its consequences for the fetus, in particular, the neurological consequences and the possible mechanisms of the effect of COVID-19 and maternal immune activation(MIA) on the nervous system. Finally, we review the interaction between fetal sex and maternal immune responses.

2. The vulnerability of pregnant women to respiratory infections, including COVID-19

Pregnant women are vulnerable to respiratory infections and pneumonia due to anatomical structure and physiological and immunological changes during pregnancy. Cardiovascular and respiratory changes, hormonal fluctuations, shortness of breath, fatigue, and changes in the immune system can increase the risk of severe respiratory infections in pregnant women [30,31]. For example, influenza infection is associated with more severe illness and death in pregnant women than in non-pregnant women, and the same is true of the previous two coronaviruses [30]. During the COVID-19 pandemic, pregnant women's susceptibility, morbidity, and mortality have increased significantly compared to non-pregnant women [11,32].

In pregnant women, the hormone progesterone is responsible for increasing the capacity of the lungs [33] and the lungs' capacity to provide more oxygen to the mother and fetus. Since the mother needs more oxygen during this time, the lungs must work harder. In the last months of pregnancy, the uterus grows and moves towards the diaphragm; the diaphragm also moves upwards (towards the lungs), and the respiratory capacity decreases; at this stage, the mother is prone to hypoxia. In addition, it causes the breathing capacity to decrease and the mother to suffer from shortness of breath [33,34]. However, increased vital volume and hyperventilation subsequently compensate for the decrease in respiratory capacity. Hyperventilation causes pregnant women to inhale more air simultaneously, making them more likely to inhale more viral particles than non-pregnant people [33,35,36].

Changes in the upper respiratory tract mucosa caused by progesterone during pregnancy lead to the attachment of the virus to the nasal mucosa and are difficult to clear [35].

Also, increased expression of ACE2 has been reported during pregnancy [33,37,38]. Studies have shown that ACE2 expression increases during pregnancy. The increased expression of ACE2 during pregnancy may be in response to regulating blood pressure during pregnancy [33]. The increased expression of this receptor could be linked to the susceptibility of pregnant women to COVID-19 [37,38].

In addition, the increase in estrogen and progesterone during the first trimester of pregnancy leads to reversible degeneration of the thymus, which could be responsible for the decrease in $CD4^+$ and $CD8^+$ T cells [38]. Changes in the immune system of pregnant women are dynamic. On the one hand, the immune system during pregnancy must be tolerogenic to preserve the allogeneic embryo. On the other hand, it must be able to fight against pathogens. During pregnancy, the immune system changes, the Th2 environment becomes dominant, and Th1-induced immunity declines. The predominant environment of Th2 and hormonal changes in pregnancy tend to increase the amount of anti-inflammatory cytokines (IL-4 and IL-10). These conditions favour developing immunological tolerance and preserving the fetus [39].

It appears that changes in the maternal immune system adapt in harmony with the stages of fetal development: in the first trimester of pregnancy, it is in a pro-inflammatory state; in the second trimester of pregnancy, an anti-inflammatory form is dominant, and in the third trimester it is also in a pro-inflammatory state [40]. A cytokine storm and an increase in inflammatory cytokines accompany severe cases of COVID-19 infection. Studies have shown that excessive increases in inflammatory responses and cytokine storms positively affect COVID-19 disease severity (an excessive rise of cytokines such as TNF-α, IL-6, IL-7, IL-2, IL-10). One of the most critical cytokines in the cytokine storm is IL-6(a cytokine associated with Th1), associated with increased severity and mortality of COVID-19 [39,41,42]. The COVID-19 infection during the first and third trimesters of pregnancy (predominance of the pro-inflammatory state) may worsen the inflammation and COVID-19 severity [43].

In sum, changes in the immune system during pregnancy are dynamic and challenging. The impact of these changes on the COVID-19 severity in pregnancy may depend on the gestational age.

In addition to the physiological and immunological changes during pregnancy, psychological changes in pregnant women should also be considered [44]. Prenatal psychosocial stress during pregnancy is common [45]; furthermore, the spread of a new infection with a high transmission rate in the form of a pandemic is likely to increase the amount of this stress in the population, particularly in pregnant women, and lead to more significant stress [44,46]. Stress affects the mother's immune system and worsens maternal inflammation [44].

3. Maternal COVID-19 infection and its fetal neurological outcomes

At the onset of the COVID-19 pandemic, studies began on the pathogenicity of the virus during pregnancy, the potential for vertical transmission, and its maternal and fetal consequences. Although there is more evidence that vertical transmission does not occur, or if it happens, its frequency is very low [47]. The absence or very low probability of an intrauterine transmission may be due to the following reasons: low levels of viremia and decreased concomitant expression of ACE-2 and TMPRSS2 (transmembrane serine protease 2) on the placenta those are required for SARS-CoV-2 to penetrate cells [48].

Psychoneuroimmunology is an attractive field in NPDs that deals with the role of immune/inflammation disturbance and its relationship with NPDs [2]. This issue can be highlighted in the context of COVID-19 because one of the main mechanisms of COVID-19 pathogenesis is immune dysregulation and excessive inflammation [15,49]. Although most evidence favours no vertical transmission of COVID-19, exposing the fetus to an inflammatory environment during maternal COVID-19 infection can affect the development of the fetus, especially the nervous system. The impact of COVID-19 on the fetus during maternal infection is still being investigated [21]. Neurological disorders are one of the possible fetal consequences of maternal COVID-19 infection [21]. Neurodevelopmental disorders such as depression, attention deficit hyperactivity disorder, cognitive dysfunction, schizophrenia, autism spectrum disorders (ASD), and anxiety have been identified following prenatal viral infections [21,50,51].

Viral infections during pregnancy can affect the fetus in two ways: First, some viruses can cross the placenta(Transmission through the placenta)and infect the fetus directly by crossing placenta, such as the Zika virus, which leads to microcephaly [51].

The second category includes viruses that do not cross the placenta, but their infection during pregnancy leads to neurological disorders in the fetus [51]. These viruses cause brain damage primarily through maternal immune activation(MIA), the activation of the placental and fetal immune systems, and then the activation of the fetal brain immune system (neuroinflammation) [50,51]. SARS-CoV-2 can potentially affect the growth and development of the fetal nervous system through maternal immune activation [52]. The flu did the same; an increased rate of neurological disorders, including schizophrenia, has been reported in adults who were fetuses during the 1957 influenza pandemic [51].

Although SARS-CoV-2 is primarily a respiratory disease [53], patients experience neurological symptoms such as headaches, dizziness, decreased consciousness, encephalitis, and encephalopathy [15,41,54]. In addition to neurological symptoms, SARS-CoV-2 has been detected in autopsy brain tissue samples from people who have died from COVID-19, suggesting that SARS-CoV-2 can attack the central nervous system. The following possible mechanisms can lead to neurological disorders in COVID-19 patients [55], as shown in Fig. 1.

(i) Systemic dysfunction and multi-organ failure: Hypoxemia in patients with severe COVID-19 may play a role in developing encephalopathy [54,56]. Additionally, metabolic disorders due to multiple organ failure may contribute to developing neurological symptoms such as uremic encephalopathy [54]. Toxic metabolic encephalopathy (TME) has been diagnosed in several hospitalized patients with COVID-19(54).

(ii) Renin-angiotensin system (RAS) dysfunction: ACE2 is a crucial component of the renin-angiotensin system, which is reduced in COVID-19 infection and causes dysregulation of the renin-angiotensin system. SARS-CoV-2 binds to ACE2 on endothelial cells and damages vascular endothelial cells [15,57].

(iii) Immune dysfunction: Cytokine storm, a phenomenon associated with increases in cytokines)such as Interleukin 6, Tumour necrosis factor α) and inflammatory mediators, have been reported in patients with severe COVID-19(15). Cytokines can cross the blood-brain barrier, leading to neuroinflammation and neurotoxic effects associated with confusion and impaired consciousness [1,55, 58]. Infectious agents can amplify inflammation and cytokine production and act as one of the etiopathogenesis factors of NPDs [2].

(iv) Direct invasion of the virus into the nervous system: The SARS-CoV-2 genome has been found in autopsy samples of brain tissue from patients with COVID-19([59]); this evidence shows the neurotropic and neuroinvasive activity of SARS-CoV-2, in addition to hematogenous spread and crossing the blood-brain barrier, neuronal dissemination may be a pathway for brain access.: after intranasal infection, some viruses infect olfactory receptor neurons, and then travel up the olfactory nerve, where they eventually reach other parts of the brain. SARS-CoV-2 may access CNS via this pathway [55].

Most evidence favours no vertical transfer, or its probability is low [47]. Therefore, the likelihood of SARS-CoV-2 directly infecting the fetus is low. However, it may affect the fetus, especially the neural development of the fetus, using the following possible mechanisms: MIA: The primary means by which SARS-CoV-2 may affect the fetus is maternal immune activation (MIA) and subsequent inflammation.

Maternal immune activation and inflammation negatively affect fetal nervous system development through several possible mechanisms, as shown in Fig. 2.

(i) Activation of the maternal immune system leads to immune system activation and inflammatory responses in the placenta and fetal brain, affecting fetal brain development. Maternal inflammation can impair fetal brain development and lead to neurological disorders [51].

Maternal immune activation is associated with elevated levels of inflammatory cytokines. Cytokines can pass through the placenta and the blood-brain barrier and impair neural development in the fetus [52]. Neurotoxic properties of Cytokines may be mediated by an increase in reactive oxygens and a decrease in monoamine transport [1]. Of course, cytokine signalling is one of the pathways through which maternal immunity influences fetal neurodevelopment.

(ii) B lymphocytes also play a role through antibody production [1]. Studies have shown that the transfer of maternal antibodies against fetal brain tissue can play a role in developing NPDs; these

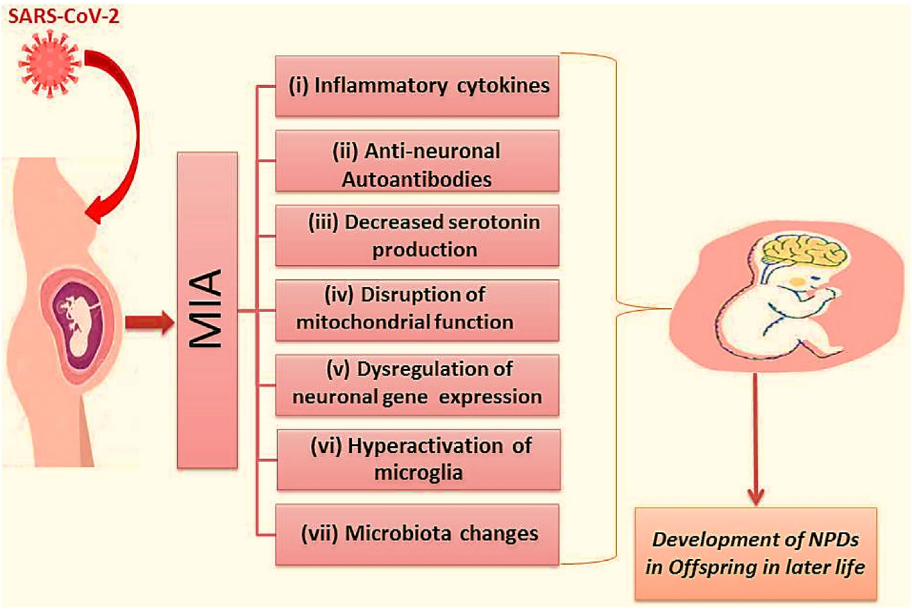

Fig. 1. Effects of maternal immune activation on fetal neurodevelopmental.

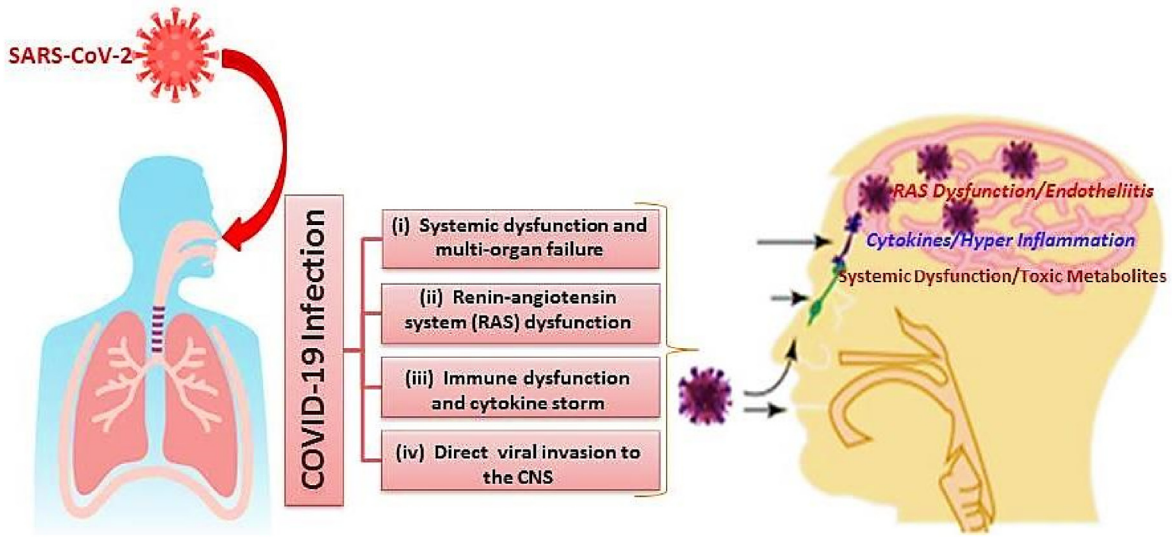

Fig. 2. SARS-CoV-2 infection in adults may affect the nervous system via the multiple mechanisms.

antibodies are probably against proteins that play a role in neurobiological processes and neurodevelopment (anti-neuronal autoantibodies) [1].

Autoantibodies can pass through the weakened blood-brain barrier and enter the brain, bind to the receptors of neurotransmitters, and thereby play a role in causing neurological disorders [60].

For example, activation of the maternal immune system is associated with increased levels of interleukin (IL)-17α, which is related to the autism spectrum phenotype and neurodevelopmental disorders [43].

Cytokine homeostasis/balance is necessary for a healthy pregnancy [52]. Interleukin-10 is required for the embryo's maintenance and immunological tolerance (the embryo is semi-allogenic). In contrast, high interleukin 1 and tumour necrosis factor-alpha (TNFα) is associated with poor pregnancy outcomes such as preterm delivery [52]. Indeed, in severe COVID-19 infection, the balance between inflammatory/anti-inflammatory cytokines is disrupted [15,61], which can harm maternal and fetal health. In another study, it was reported that the increased levels of cytokines IL-1β, IL-8, and CRP are related to neurodevelopmental morbidity such as microcephaly [62]. Animal studies have shown that interleukin-6 is a central inflammatory mediator that affects fetal brain development [1].

(iii) The placenta is the source of serotonin, which is necessary for the development of the fetus's brain [51]. Activation of the maternal and placental immune systems and inflammation disrupt serotonin signalling pathways [1]. Disruption of serotonin signalling affects brain development by reducing synaptogenesis [51]. In addition, disturbance of the signalling way of other neurotransmitters has also been reported following activation of the maternal and placental immune systems.

(iv) Activation of the maternal and placental immune systems can lead to disruption of mitochondrial function in the fetal brain and increased oxidative stress [51].

(v) MIA can also lead to the dysregulation of gene expression related to the nervous system's development [1].

(vi) MIA leads to the hyperactivation of microglia [63]. As cells of innate immunity, microglia are located in the brain parenchyma and play an essential role in the homeostasis of synaptic circuits in the CNS(1). Although microglia are critical for normal brain function, their overactivity has been linked to detrimental effects on the nervous system [1].

(vii) Maternal immune activation can affect the composition and function of the maternal microbiota [51] as the microbiota during childbirth and breast milk is transferred to the fetus and infant. Hence, the change in the maternal microbiota leads to the difference in the infant's microbiota. The microbiota and metabolites can influence children's brain function via the microbiota-gut-brain axis [51].

In addition to the effects of MIA on the nervous system, other mechanisms affect neurodevelopment: fever is one of the most common symptoms in COVID-19 patients [15], which has been reported to be associated with an increase in attention-deficit/hyperactivity disorder in children [50]. For example, although the influenza virus cannot cross the placenta, influenza infection is often associated with fever, and fever may explain neurological disorders in infants born to mothers with influenza [50].

Hypoxia and hypoxemia following severe COVID-19 infection are reported in some patients. A study found severe fetal brain damage after hypoxemia in a pregnant mother with COVID-19([64]).

Physiological and psychological changes during pregnancy increase perinatal stress and anxiety [65]. In addition, the COVID-19 pandemic has increased the stress level in pregnant women more than before [44, 65]. Factors such as adherence to new health protocols, and the need for a negative PCR test for COVID-19 at the time of delivery, caused more stress in pregnant women [65].

Increased stress and anxiety during pregnancy affect the mother's immune system and increase maternal inflammation [44]. Maternal stress and inflammation affect fetal brain development and can cause neurological complications in the child [44,46].

Animal studies show increased perinatal stress can lead to decreased myelin and structural changes in dendrites [66]. In addition, exposure of the fetus to the hormone cortisol (stress hormone) may lead to structural and functional changes in the brain [67].

Another consequence of stress during pregnancy is preterm delivery [68]. One of the most critical complications of maternal COVID-19 infection is preterm birth [39]. Preterm birth is associated with the risk of neurodevelopment in infants [51]. Neural development of the fetus begins from the third week of pregnancy and continues into adulthood [69]. However, in the case of preterm birth, although the infant's neural development continues after birth, the environment outside the womb for neural development is very different from the dark, quiet environment. In such a situation, premature birth can adversely affect the neural development of the fetus.

4. The effect of maternal COVID-19 infection on the fetal immune system

The fetal immune system is trained in various ways by the mother's immune system [70,71]. One of the most well-known ways is to transfer maternal antibodies through the placenta to the fetus [72]. In addition to antibody delivery, the mother affects the fetal immune system through microbial exposure and inflammation [71]. Maternal inflammation and infection can affect the fetal immune system in the following ways: First, an infectious agent directly infects the fetus (intrauterine transmission). Second, maternal inflammatory cytokines cross the maternal-fetal interface and enter the fetal environment. Third, infectious antigens (not infectious pathogens) can cross the placenta by attaching to antibodies and entering the fetal environment, thereby affecting the immune system. One study hypothesized that fetal hematopoietic stem cells receive infection and microbial signals, affecting the fetal immune system and beyond [71].

Maternal infection with hepatitis C and HIV viruses during pregnancy can also affect fetal immune system development, even without vertical transmission [73]. Evidence has been observed that COVID-19 infection in pregnant mothers can affect the fetus indirectly.

In this regard, researchers studied the immune system of infants born to mothers with COVID-19 infection. In one study, COVID-19 infection in pregnant women triggered a cytokine response in the fetal umbilical cord and blood. In these infants, elevated levels of cytokines IL-17A and TNF were observed in cord blood. Moreover, no IgM antibody was observed in the umbilical cord blood of infants, which confirms the lack of vertical transmission [74].

Gee et al. showed that exposure of the fetus to maternal COVID-19 infection -without congenital infection - can affect fetal immune system development [73].

Increased proportions of natural killer cells, Vδ2 + γδ T cells, and regulatory T cells were found in infants born to COVID-19-infected mothers compared to convalescent or non-infected mothers. Elevated plasma cytokine levels were observed in mothers exposed to COVID-19 and their infants. In addition, cytokine function was higher in infants born to mothers exposed to SARS-CoV-2 than in infants of uninfected mothers [73].

This evidence suggests that SARS-CoV-2 activates the maternal immune system and leads to fetal inflammation and activation of the fetal immune system. Indeed, exposure of the fetus to an inflammatory environment (not necessarily through direct infection of the fetus) appears to have the potential to adversely affect fetal growth and the immune system [75].

Activation of the fetal immune system and the formation of multifunctional immune cells may harm the colonization of the intestinal microbiota at birth. The infant's immune system needs to be hypofunctional and tolerogenic at birth for normal gut microbiota colonization. If the immune system is activated, polyfunctional immune cells may prevent the proper colonization of microbes in the gut, leading to severe inflammatory intestinal disease. For example, necrotizing enterocolitis has been reported in some neonates born to mothers with the SARS-CoV-2 infection [75].

Maternal SARS-CoV-2 infection causes changes in the fetal immune system, such as changes in the number of immune cells and cytokines. Even after the mother's infection clears, changes in the fetal immune system remain, leaving evidence of multifunctional immune cells. What is worrisome is that these inflammatory changes affect fetal nervous system development [75].

5. The possible effect of fetal sex on maternal and placental immune responses

Sexual dimorphism has been proven in COVID- 19 disease [42]. Men are at increased risk of COVID-19 infection and mortality [76]. Sexual dimorphism has also been reported in various pregnancy complications. For example, a male fetus is associated with an increased risk of preterm birth, or gestational diabetes is more common in women with male fetuses [77,78]. Cardiovascular and metabolic diseases are also more common in mothers with male fetuses [78]. A female fetus was associated with a higher risk of pre-eclampsia; however, the data in this regard are inconsistent [79]. In recent years, the hypothesis of the effect of fetal sex on the mother's immune environment has been reported [32].

Given that there are differences in sex-based immune responses throughout human life, it seems that the issue of the effect of fetal sex on maternal immune responses should be further evaluated [80]. One of the main factors in developing fetal and infant immunity is the transfer of maternal antibodies through the placenta and breast milk, which protects the infant in the first months of birth against infections. Maternal IgG antibodies enter the fetal circulation through the placenta. After childbirth, the maternal IgA antibody in breast milk is passed to the neonate to protect it from respiratory and gastrointestinal infections [81,82].

In this regard, Bordt et al. [83] examined the effect of fetal sex on maternal and placental immune responses to SARS-CoV-2. Their study showed that fetal sex affects the immune response of the mother and placenta to SARS-CoV-2. Mothers with male fetuses have reduced immune responses compared with mothers with female fetuses. In mothers with a male fetus, a decrease in the titer of the mother SARS-CoV-2-specific antibody and a decrease in the transfer of antibodies through the placenta were observed.

Available data suggest that immune system activation/dysregulation is a significant cause of tissue damage in COVID-19([84]). In this regard, the impact of fetal sex on immunological responses during pregnancy may affect the pathogenicity of SARS-CoV-2 in pregnant women [85]. We hypothesize that male fetuses may affect maternal COVID-19 disease severity by reducing maternal immune response compared with female fetuses. Of course, this is a complex issue, and it is impossible to draw a complete conclusion based on the available information; it is required to examine the data on COVID-19 disease severity in the pregnant mother and its relationship with the sex of the fetus. It opens an important field of research.

Suppose the male fetus reduces maternal antibody/humoral responses, so less antibody crosses the placenta. It is also possible that fewer IgA antibodies are produced in the mother's body, which can result in fewer IgA antibodies being transmitted to the male infant by breast milk. Therefore, the male infant receives less IgG and IgA than the female infant. Thus, decreased maternal antibody transmission to the male fetus and infant may be associated with increased male infant mortality due to infections.

On the other hand, the results of the above study raise this question: does fetal sex affect the vaccine response of pregnant mothers? If the sex of the fetus affects the mother's immune response, it may also affect the mother's response to the vaccine during pregnancy. Studies on the possible association between response to the COVID-19 vaccine in pregnant women and fetal sex are needed to clarify this question.

6. Conclusion

Maternal COVID-19 infection affects the fetal immune and nervous systems. Although SARS-CoV-2 does not directly infect the fetus, exposing the fetus to an inflammatory environment activates the fetal immune system. Maternal and placental/fetal immune activation can affect fetal nervous system development.

The impacts of the COVID-19 pandemic can be seen in the short and long term. For example, preterm delivery is a short-term complication during the pandemic. However, on the other hand, the effects of maternal COVID-19 infection on the fetal nervous system can manifest themselves in the long term - a generation with a higher risk of developing neurological disorders in the future. Because the effects of maternal infection may be seen on children in the long term, the risk of maternal disease and maternal immune activation may be underestimated. Given the above, longitudinal monitoring or long-term surveillance of children born

during the COVID-19 pandemic is recommended to identify the risk of neurological disorders and timely treatment.

Founding

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Author contribution

Sh. F, A. A and A. K equally have a role in Conceptualization, Methodology and wrote the main manuscript text.

Data availability statement

Not applicable.

Declaration of competing interest

The authors have no conflicts of interest to declare for this study.

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