

SARS-CoV-2 Infection in Pregnant Women: Neuroimmune-Endocrine Changes at the Maternal-Fetal Interface

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Keywords

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has devastating effects on the population worldwide. Given this scenario, the extent of the impact of the disease on more vulnerable individuals, such as pregnant women, is of great concern. Although pregnancy may be a risk factor in respiratory virus infections, there are no considerable differences regarding COVID-19 severity observed between pregnant and nonpregnant women. In these circumstances, an emergent concern is the possibility of neurodevelopmental and neuropsychiatric harm for the offspring of infected mothers. Currently, there is no stronger evidence indicating

vertical transmission of SARS-CoV-2; however, the exacerbated inflammatory response observed in the disease could lead to several impairments in the offspring's brain. Furthermore, in the face of historical knowledge on possible long-term consequences for the progeny's brain after infection by viruses, we must consider that this might be another deleterious facet of COVID-19. In light of neuroimmune interactions at the maternal-fetal interface, we review here the possible harmful outcomes to the offspring brains of mothers infected by SARS-CoV-2.

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Introduction

The coronavirus family has been described in the mid-1960s, affecting humans and animals. In 2002, the first case of a severe human respiratory infection (severe acute respiratory syndrome [SARS]) was reported in Foshan, China. New cases emerged from 2003 in Mainland China,

spreading to Hong Kong, Vietnam, and Canada, totaling 8,096 reported cases, including 774 deaths in 27 countries [1–4].

A second event (of the disease) in humans occurred in 2012 [5]. The coronavirus strike started this time in Saudi Arabia, expanding into several countries and causing what is now known as coronavirus Middle East respiratory syndrome (MERS-CoV). Until February 2019, 2,279 confirmed cases of MERS-CoV were reported, including 806 deaths [6].

Less than 10 years after the SARS epidemic, the world watches in disbelief the third strike of coronavirus causing a highly contagious viral pandemic pneumonia denominated coronavirus disease 2019 (COVID-19). Similar to SARS in 2002, the first cases of COVID-19 that occurred from a zoonotic transmission in China in December 2019 are linked to the wildlife and seafood trade. Spreading rapidly within China and quickly to other countries, COVID-19 reached 195 countries and infected >100,200,107 people, causing >2,158,761 deaths by January 28, 2021 [7, 8].

The novel coronavirus denominated SARS-related coronavirus 2 (SARS-CoV-2), now officially known as the cause of COVID-19, carries RNA genomic sequences similar to other coronaviruses, mainly related to SARS-CoV RNA [9]. However, the clinical symptoms related to both viruses are quite distinct. In the context of a severe case of COVID-19, a picture of multiple organ dysfunctions (MODS) has also been observed, and some authors would even suggest the change in typification from SARS to MODS [10]. Furthermore, mechanisms leading to MODS in COVID-19 seem to be related not only to the viral load that accumulates in several organs but also to the exacerbated inflammatory response (“cytokine storm”) triggered by SARS-CoV-2 infection [10]. Although there are many issues to be properly addressed, knowledge of the mechanisms of infection, the clinical course of the disease, inflammatory markers, prognosis, disease complications, and mechanical ventilation strategy is rapidly growing [11, 12].

The broad extent of COVID-19 harm generated a major concern about more vulnerable populations. Currently, there is great interest in pregnant women COVID-19 infection and the possible impairments on the health of their babies. Although studies on COVID-19 have rapidly advanced, the effects of SARS-CoV-2 on fetal development remain unclear. Little is known about vertical transmission in COVID-19. Despite evidence indicating placental and fetal infection [13], this subject is under great discussion in the scientific community and is still controversial.

Pregnant women are especially susceptible to pathogens. The maternal-fetal interface barrier offers protection to the fetus, and when it fails, pathogens breach the innate maternal immune system and placental trophoblastic host defenses to infect the fetus by mechanisms not completely elucidated. Based on knowledge of other viruses, such as herpesviruses (varicella), Rubivirus (rubella), flaviviruses (hepatitis C, dengue, Zika virus [ZIKV]), hepadnavirus (hepatitis B), lentivirus (HIV), and parvoviruses, it is known that they are capable of circumventing placental defenses to cause detrimental and sometimes lethal effects on the fetus [14]. These effects include target organ damage (microcephaly, intracerebral calcifications, hepatosplenomegaly, chorioretinitis, microphthalmia, and deafness), fetal compromise (miscarriage, growth restriction, hemolytic anemia, and hydrops), and death [14]. All these information about other viruses rises in us a flag on the extent of SARS-CoV-2 damage to fetal development. In the case of the SARS epidemic in 2002/2003, for instance, several reports showed that clinical outcomes were worse in pregnant women than in nonpregnant women; there was an increase in abortion rates and premature births associated with SARS-CoV infection [15].

Recent studies have described that infected pregnant women have inflammatory, thrombotic, and vascular changes, suggesting that the inflammatory nature of SARS-CoV-2 infection during pregnancy can cause adverse obstetric and neonatal events [13]. Independently of a possible vertical transmission, the exacerbated maternal immune response could trigger serious consequences for fetal development, mainly on neurodevelopment. This pandemic scenario is too recent for proper long-term evaluation of its consequences in this special population. However, in the face of historical evidence of viruses causing acute and long-term consequences to mother and progeny, we must consider the outstanding possibility that this might also be another deleterious facet of COVID-19. In this context, we discussed possible harmful neurodevelopmental and neuropsychiatric outcomes in the offspring of mothers infected by SARS-CoV-2 in light of neuroimmune interactions at the maternal-fetal interface.

Neuroimmunological Aspects of SARS-CoV-2 Infection

In patients with COVID-19, the general clinical manifestations observed are respiratory failure, lymphopenia, monocyte and macrophage infiltration in lung lesions,

hypercoagulability, thrombosis, and multiple organ failure (in severe cases). Moreover, all symptoms are accompanied by an inflammatory cascade, making evident a viral infection-related inflammation and its characteristic “cytokine storm,” which, in severe cases, plays a crucial role in the clinical manifestations [16, 17]. The uncontrolled inflammation that seems to affect the lungs could also affect other systems, including the nervous system [10, 18]. Accordingly, clinical studies revealed that the brainstem respiratory center is the main target of SARS-CoV-2 in the central nervous system (CNS), leading to dysfunction and consequent acute respiratory distress in individuals with COVID-19 [19]. The “cytokine storm” observed mainly in individuals with severe COVID-19 is marked by the uncontrolled production and release of inflammatory cytokines and chemokines (e.g., interleukins [IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18, IL-33], tumor necrosis factor alpha, interferons [IFN- α , IFN- γ], granulocyte and macrophage colony-stimulating factor [CSF], macrophage inflammatory protein 1 alpha, platelet-derived growth factor, monocyte chemoattractant protein 1) by activated macrophages, neutrophils, monocytes, lymphocytes, natural killer (NK) cells, and dendritic cells (DCs) [11, 20–26].

Systemically, after SARS-CoV-2 infection, an initial innate immune response takes place, leading to activation and differentiation of T cells by the adaptive immune system. This, in turn, plays an important antiviral role in an effort to balance the response of the immune system against the pathogen and the exacerbation of inflammation [27]. Accordingly, CD4⁺ T cells lead to the production of specific antibodies against the virus by B lymphocytes, while CD8⁺ T cells are cytotoxic and can kill virus-infected cells. In addition, pro-inflammatory cytokine and chemokine production is important for the recruitment of lymphocytes, monocytes, and neutrophils to the site of infection, causing an amplification of the inflammatory response [16].

The main mechanism described for SARS-CoV-2 entry into human host cells (including CNS cells) is a receptor-mediated mechanism. Indeed, several studies suggest that the SARS-CoV-2 spike glycoprotein binds to its cell receptor angiotensin-converting enzyme 2 (ACE2) in the host cell membrane along with transmembrane serine protease 2, which is responsible for the priming of viral S glycoprotein, facilitating its entrance into the cell and promoting moderate replication with a continuous release of virions from infected cells [28]. The ACE2 and transmembrane serine protease 2 receptors are expressed in the olfactory mucosa and neurons in humans and glial

cells in mice. The expression of both receptors is increased in the murine model with age, fueling a discussion whether the elderly may be at greater risk due to the accumulation of SARS-CoV-2 in these cells [29, 30]. In this context, CNS invasion mechanisms are not fully elucidated, although some potential routes have already been described. For instance, viremia may result in viral transcytosis through the blood-brain barrier (BBB) endothelial cells or epithelial cells in the choroid plexus surrounding the cerebral ventricles. In addition, SARS-CoV-2 could enter via the olfactory nerve and other peripheral nerves, such as trigeminal fibers and/or the vagus nerve, which innervate different parts of the respiratory tract, including the larynx, trachea, and lungs [31–33].

Once in the CNS, SARS-CoV-2 could trigger a local inflammatory cascade stimulating the release of inflammatory mediators by local cells. In addition, it is important to note that the exacerbated systemic release of cytokines and chemokines may increase blood-brain barrier permeability and promote the activation of neuroinflammatory cascades, facilitating leukocyte migration to the CNS and SARS-CoV-2 invasion [34, 35]. The dysregulated cytokine release in the CNS also promotes neuronal hyperexcitability via activation of glutamate receptors and leads to an acute form of seizures, for example [36, 37]. It has been suggested that the exacerbated immune system response in COVID-19 can lead to inflammatory lesions and edema in the brain [38].

Moreover, neurological clinical signs such as loss of smell and taste [39–43], headache [20, 44, 45], seizures [46], strokes [47], and meningitis/encephalitis [48] have also been reported in patients with COVID-19. There is already a growing body of evidence showing patients presenting both neurological and psychiatric (e.g., anxiety and depression) outcomes after infection [26, 49]. Furthermore, the role of neuroinflammation in several psychiatric disturbances is well established in the literature and could well be the main cause of such impairments observed in COVID-19 [26]. Nevertheless, more studies are necessary to strengthen this relationship in COVID-19.

Pregnancy and SARS-CoV-2 Infection

Physiological Immune-Endocrine Changes at the Maternal-Fetal Interface

The mother’s body needs to adapt in order to support the growth and development of the hemiallogeneic fetus. The maternal-fetus interface is formed of a mucous mem-

brane originated from differentiated endometrial cells, or decidua, at the beginning of pregnancy involving the fetus, umbilical cord, and placenta. This interface promotes tolerance and local defense against infections and pathogens [50–54]. Immune responses at the maternal-fetal interface need to support reception, establishment, and growth since the implantation of blastocyst until birth [55]. Fetal trophoblastic and maternal decidual immune cells interact at the maternal-fetal interface, allowing the embryo to develop in the uterus [56].

The postimplantation tissue is rich in immune cells such as leukocytes, macrophages, DCs, and T cells [57, 58]. For this reason, it was initially believed that the blastocyst triggers a maternal immune response destined for its rejection. The fetal placental unit expresses proteins of paternal origin, and for this reason, it was believed that for pregnancy to occur, the maternal immune system should be constantly suppressed. However, immune infiltrates are required to facilitate proper implantation, to maintain tolerance, and to promote a successful pregnancy [55].

The proportion of decidual immune cells vary according to the cell type and the trimester of pregnancy. NK cells represent approximately 70–80% of leukocytes at the maternal-fetal interface, macrophages are 20–25%, DCs are 1.7%, and T cells 3–10% [57, 58]. NK cells and macrophages are especially high in the first trimester of pregnancy and decrease in the second and third trimesters. On the other hand, T cells are few in the first trimester and increase in the third trimester. These changes, in proportions, are related to the functions they perform [54].

Decidual NK (dNK) cells are the most abundant leukocytes in the first trimester and play important roles in early pregnancy events. dNK cells regulate the invasion of fetal trophoblast cells in the decidua [59, 60] and arterial remodeling [61–63]. They accumulate around maternal uterine spiral arteries (SAs) before trophoblast invasion, favoring the remodeling of the SAs needed to support fetal growth [64]. dNK cells produce cytokines such as tumor necrosis factor alpha, IL-10, IL-1 β , IL-6, IL-8, TGF- β , IFN- γ , macrophage-CSF, and granulocyte-macrophage CSF. dNK cells also produce angiogenic growth factors such as vascular endothelial growth factor-C, placental growth factor, angiopoietin-1, and proteases such as matrix metalloproteases [65–70].

Macrophages are the second most abundant population of leukocytes in the early period of pregnancy, performing a variety of essential functions [71]. They are related to the remodeling of blood vessels [63, 72, 73], trophoblast invasion [74–76], tolerance [76, 77], immunomodulation of maternal lymphocytes, and parturition

initiation through the production of pro-inflammatory cytokines and prostaglandin E2 [76, 78–80]. Macrophages have an M1 profile during the peri-implantation period, changing to an M1/M2 profile when the trophoblasts invade the uterine stroma and fixate on the endometrium, allowing the placental-fetal blood supply to be adequate during the first trimester and the beginning of the second trimester [81]. Then, the deciduous macrophages change to a predominantly M2 polarity that will prevent rejection of the fetus and allow it to develop until delivery. This tolerance to the fetus occurs especially by the production of IL-10 [71, 77, 82, 83], prostaglandin E2 [71, 84], enzymatic activity of indoleamine 2,3-dioxygenase [71, 77], and TGF- β [71] by macrophages.

Although present in a much lower concentration than macrophages in decidua, DCs are also involved in maintaining tolerance to the fetus. DCs are found in the placental bed in both their mature and immature forms; however, the number of immature cells is much higher [85]. They undergo partial inactivation and decrease in size in the third trimester [86]. This immature state has the main function of maintaining immunological tolerance [87]. Immature DCs (DC-SIGN + iDC) can induce Treg cells during pregnancy, reinforcing their role in inducing tolerance against fetal antigens [88].

The functions of T cells during pregnancy are still not fully understood. In the first trimester, trophoblast cells produce the chemokine CKCL16 that interacts with the CXCR6 receptor of T cells, attracting circulating T cells to decidua, forming a specific microenvironment [89]. Thus, deciduous T cells, in addition to regulating the placental microenvironment, recognize fetal antigens, without attacking them [54]. This recognition occurs through the interaction with antigen-presenting cells in the decidua, promoting tolerance to the fetus during pregnancy [90]. T cells that are suppressed during pregnancy increase next to labor; they infiltrate the maternal-fetal interface before and during delivery [91]. The decidual T cells have activation markers and mediators implicated in both term and preterm labor, indicating that these cells participate in this process [92].

In short, pregnancy is a pro-inflammatory environment during the first trimester, enabling implantation and placentation, then shifts to an anti-inflammatory stage, allowing fetal growth during the second trimester and finally shifts back to a pro-inflammatory stage that promotes labor and delivery during the third trimester [55]. From these perspectives, physiological changes and possible alterations at the maternal-fetal interface concerning SARS-CoV-2 infection will be further discussed.

The Neuroimmune Changes Caused by SARS-CoV-2 in Pregnant Women

Immune mediators such as cytokines, chemokines, and neurotrophins actively participate in the development of the CNS by regulating neuronal and glial cell migration, differentiation, survival, synaptogenesis, synaptic maturation, plasticity, and programmed cell death [93–98]. Changes or interruptions in these pathways can not only affect neurodevelopment but also impair cognitive and intellectual abilities after birth. In addition, it has been widely demonstrated that disturbances in these pathways can increase the risk of psychiatric disorders [98–100].

In early periods of development, microglia are the main source of cytokines in the CNS. Microglial cells are macrophage-like cells responsible for the innate immune response in the CNS [101–103]. They respond to pathogens, infections, or cell damage [104]. Of hematopoietic origin, they colonize neural structures at embryonic ages in the late first trimester in humans [105–108]. Microglia enter the parenchyma via the bloodstream and migrate throughout the CNS, becoming self-renewing [103, 108–110]. Thus, the activation of microglia can alter the profile of immune mediators produced in the CNS and therefore impact neurodevelopment [93, 94, 108].

The particularities of pregnancy make pregnant women a risk group for infections such as those caused by viruses [111]. Notably, interference in the inflammatory state can have consequences for the mother and the developing fetus [55]. Hormone levels and the immune response show variations during pregnancy; for example, early pregnancy seems to be more susceptible to adaptive changes in response to fetal antigens, but the mother's endocrine and immune response tends to become more balanced and stable in the final stages of pregnancy. The crucial period of fetal organ development is early pregnancy, and the immune system is off balance at this stage. For this reason, fetal organ development is particularly sensitive to infections in this period [112].

The current COVID-19 pandemic is still recent, and cases of COVID-19 during pregnancy have been reported. Despite the small amount of information available, it is already clear that infection by SARS-CoV-2 induced a relevant disturbance in the immune response of pregnant women.

Viruses and bacteria can use toll-like receptors and NOD-like receptors expressed by immune cells. Maternal infections, such as sepsis, can cause damage to the fetus CNS by mechanisms that involve the activation of microglia. To fight a current infection, the pregnant woman

immunological mechanisms increase the secretion of pro-inflammatory cytokines capable of crossing the placental barrier. These cytokines induce activation of the fetal microglia, dysregulating the production of cytokines in the fetus. In fact, inflammatory cytokines such as IL-6, IL-17, and IL-1 β are elevated in CNS after birth in animals exposed to prenatal infection. This mechanism could be linked to psychiatric disorders in the offspring [113].

Severe COVID-19 patients show signs of viral sepsis. Neutrophils and neutrophil-derived extracellular traps (NETs) are critical for sepsis pathogenesis [114–116]. Veras et al. [117] demonstrated that patients with severe COVID-19 have increased levels of NETs in the plasma and tracheal aspirate. NETs were equally found in the lung tissue from autopsies of COVID-19 victims. SARS-CoV-2 also induces the *in vitro* release of NETs by activating arginine deiminase 4 (PAD-4) in healthy neutrophils. In this way, the number of circulating neutrophils could be used as a marker of severity for patients with COVID-19 [117, 118]. It is conceivable that a similar mechanism could be operating in pregnant women with COVID-19.

Fever and cough were the most common symptoms reported in the literature [119–126], but lymphopenia and increased levels of C-reactive protein were also frequent [119–123, 125, 127–131]. Other laboratory findings showed increased concentrations of alanine aminotransferase and aspartate aminotransferase (AST) [120], increased neutrophil count, and no differences in IL-6 levels [128]. Most pregnant women infected with SARS-CoV-2 developed mild to moderate COVID-19 pneumonia [120–122, 128, 130]. Severe pneumonia occurs rarely and is related to neonatal death [119].

Abortions can be caused by different mechanisms; among them, infections are the most reported [132]. SARS-CoV-2 infection is related to acute inflammation of the placenta. Baud et al. [133] described a case of an obese 28-year-old pregnant woman in Switzerland. The patient had high fever (102.5°F [39.2°C]), myalgia, fatigue, mild pain when swallowing, diarrhea, and dry cough but no pneumonia. The stillborn infant tested negative for SARS-CoV-2, and fetal autopsy showed no malformations. However, the placenta was positive for SARS-CoV-2. Placental histology showed infiltrates of neutrophils and monocytes, in addition to funisitis (inflammation of the umbilical cord connective tissue, which indicates an inflammatory response in the fetus) [133]. Another reported case was that of a previously healthy 35-year-old woman also presenting fever and classical symptoms of

COVID-19. SARS-CoV-2 infection was confirmed by laboratory tests. Histological examination of the placenta showed inflammatory infiltrates with macrophages and T lymphocytes, in addition to the presence of diffuse perivillous fibrin. SARS-CoV-2 was located in syncytiotrophoblast cells [134].

A study conducted at the Johns Hopkins Hospital (JHH) showed that pregnant women infected with SARS-CoV-2 have high concentrations of IL-1 β , but not IL-6, in blood samples. This pattern was similar to that found on the fetal side of the placenta, especially in asymptomatic pregnant women. In addition to placental infection, pregnant women with SARS-CoV-2 infection showed reduced viral antibody response with reduced anti-S-receptor-binding domain IgG and less neutralizing antibody detectable. The transfer of maternal nAb via placenta was also inhibited by SARS-CoV-2 infection. Notwithstanding this, long-term implications of placental inflammation in postnatal life need to be investigated [135]. Besides, placental histopathology has already been associated with neurodevelopmental disabilities such as autism spectrum disorders (ASDs) and attention-deficit/hyperactivity disorder (ADHD) [136, 137].

Preterm births have been reported in pregnant women infected with SARS-CoV-2 [120, 121, 130, 138, 139]. Viruses are capable of changing the trophoblast cell response to commensal bacteria from the microbiota present on the mother-fetus interface. Under normal conditions, these cells secrete IFN- β , which influences receptivity to the fetus and can prevent vertical transmission of virus [140]. Viral infections decrease the levels of IFN- β from trophoblastic cells, changing the inflammatory profile of the mother-fetus interface. As a consequence, viruses impair fetal receptivity and increase the chance of preterm birth [141]. The onset of labor includes cytokines and chemokines secretion from immune cells that infiltrate and reside at the maternal-fetal interface [142]. Thus, the potential activation of inflammatory pathways by SARS-CoV-2 may result in preterm birth.

Several studies reported that COVID-19 symptoms can be intensified after labor. A study conducted with 8 pregnant patients, 6 laboratory-confirmed SARS-CoV-2 infections and 2 highly suspected SARS-CoV-2 infection cases, and 5 pregnant cases excluding SARS-CoV-2 infection admitted to the Maternal and Child Health Hospital of Hubei Province, Wuhan, China. The patients with SARS-CoV-2 were all in the third trimester, and their ages ranged from 26 to 35 years. Before labor, 87.5% of the patients had no fever or cough. Three of the 7 patients developed fever and typical ground-glass opacities in the

lungs at 1 or 2 days postpartum. Only 1 patient had fever and typical ground-glass opacities on prepartum admission. White blood cell counts, lymphocytes, and C-reactive protein of all patients were normal or slightly higher before labor. On the other hand, they had increased white blood cell counts and C-reactive protein levels, and lymphopenia occurred in 62.5% of the pregnant women after labor [143].

The effects of SARS-CoV-2 on pregnancy are still unclear. Studies suggest that pregnant women are generally in a risk group for infectious diseases (including COVID-19) due to immunological and hormonal changes at this period [144, 145]. In fact, patients with COVID-19 present activation of both Th1 and Th2 axis, resulting in increased levels of IFN- γ and IL-1 β , in addition to IL-4 and IL-10 [11]. This feature can favor the immune response to SARS-CoV-2 in pregnant women, which may result in a lower severity when compared to nonpregnant individuals [120].

SARS-CoV-2 Infection-Related Neuroimmune-Endocrine Alterations over Pregnancy

Maternal infections by viruses have been extensively reported to lead to several neuropsychiatric outcomes (e.g., psychosis, depression, anxiety, schizophrenia spectrum disorders, cognitive deficits, and sensory-motor deficits) [146]. Furthermore, abnormal levels of inflammatory mediators [147, 148] and steroid hormones [149] after prenatal infections can lead to disruption in fetal development. In addition, it was recently proposed that the increased levels of cytokines observed in COVID-19 may lead to dysfunctions in the negative feedback between hypothalamic-pituitary-adrenal (HPA) axis (hyperactivity or hypoactivity) and immune system, which could be behind mental health disturbances found in COVID-19 patients [26]. Since acute infections can potentially activate the HPA axis, SARS-CoV-2 infection-related hormonal changes are expected to modulate the maternal-fetal interface as well as producing long-term neuronal effects.

In light of a neuroendocrine-immune concept, the placenta is far more than an organ for protection and nutrition connecting mother and fetus [150, 151]. The mother's placenta displays a substantial complexity acting as a neuroendocrine organ, capable of secreting neuroactive signaling factors (e.g., oxytocin, melatonin, serotonin, and thyrotropin-releasing hormone), steroid hormones (e.g., progesterone, estrogens, and glucocorticoids), growth hormones, and others. These signaling factors can act through autocrine, paracrine, and endocrine path-

ways, which could reach the maternal and fetal circulation, promoting fundamental regulatory functions [150, 151]. During pregnancy, neuroendocrine-immune interactions become even more complex. The maternal, fetal, and placental HPA axes (an important regulatory mechanism of excessive production of inflammatory mediators through the release of glucocorticoids [e.g., cortisol]) work in an integrated manner to avoid any adverse effects of stressors on both mother and offspring [151].

In the course of pregnancy, the levels of maternal glucocorticoids and progesterone increase and are essential for pregnancy maintenance, as low levels of progesterone have been associated with preterm labor [152] and spontaneous miscarriage [153]. It is noteworthy that progesterone can also shift the cytokine balance of immune responses toward an anti-inflammatory profile and may induce the expansion of regulatory T cells (CD4⁺ and CD8⁺) at the maternal-fetal interface [154, 155]. There is evidence that H1N1 influenza virus infection in pregnant mice disrupts the production of progesterone and placental architecture (increased regions of fetal endothelial cell death, degradation of the spongiotrophoblast layer, and fibrinoid necrosis in the maternal decidua layer) and dysregulates inflammatory responses, promoting preterm labor, impairment of fetal growth, and increased fetal mortality [156]. In this context, it seems reasonable to presume that SARS-CoV-2 infection in pregnant women may also lead to disruptions of progesterone production, which in turn could generate major complications for fetal development and health.

As progesterone, balanced levels of glucocorticoids during pregnancy are essential for suitable fetal brain development. As cited above, the infection by SARS-CoV-2 has been proposed to unbalance HPA axis activity [26], which raises concern about the pregnant women population. To protect the fetus from excessive exposure to these hormones throughout gestation, a mechanism such as the fetoplacental expression of the glucocorticoid-inactivating enzyme 11 β -hydroxysteroid dehydrogenase type 2 (an enzyme that metabolizes bioactive cortisol into bioinactive cortisone) is elicited [149]. Under some circumstances, as high fetus exposure to glucocorticoids evoked by stressors (e.g., maternal infections and/or excessive exposure to inflammatory mediators), this regulatory mechanism can be disrupted; potentially triggering a mechanism termed fetal or developmental “programming” [149, 157, 158]. Early life programming increases the fetus susceptibility to diseases including neuroendocrine and psychiatric disorders in adulthood [159] and influences adult behavior and HPA axis responses [157].

In this respect, we can propose, and it will not be surprising, that SARS-CoV-2 may damage fetal brain development and lead to neuropsychiatric disturbances in childhood or adulthood by fetal “programming” triggered by excessive exposure to maternal glucocorticoids.

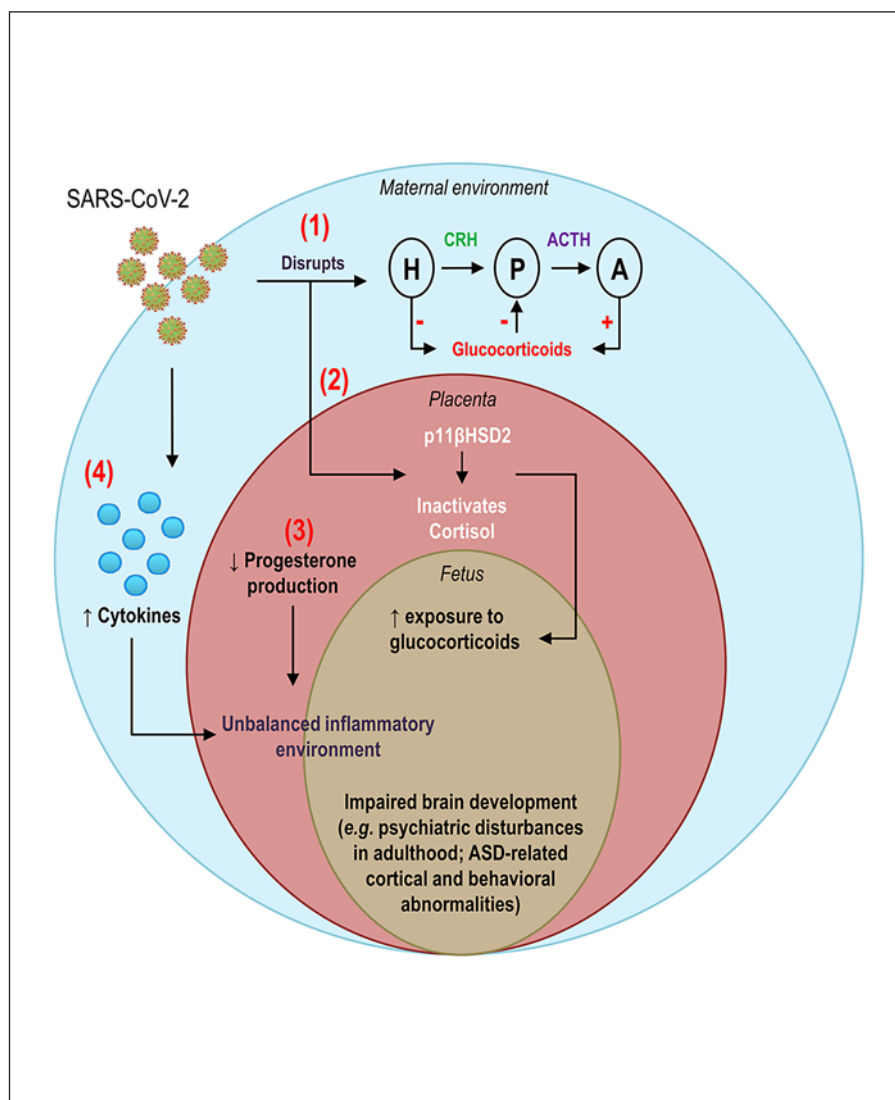
Of note, since cross talk between inflammatory mediators and steroid hormones in the placenta is crucial for proper fetal brain development [160], we hypothesize that the exacerbated inflammatory response triggered by SARS-CoV-2 infection could also disrupt such interactions and impair the offspring’s neurodevelopment. Correspondingly, maternal inflammation is thought to result in elevated pro-inflammatory cytokines that can cross the placental barrier and access placental cells via maternal blood in the SAs and intervillous spaces, influencing the fetal brain development [160]. Studies have shown that maternal immune activation (MIA) induced sustained alterations in motility patterns of fetal microglia, which may contribute to subsequent risks for cognitive diseases [161]. Moreover, it has been demonstrated that MIA may lead to an increase in Th17 cells in maternal serum, which can be associated with ASD-related cortical and behavioral abnormalities in the offspring [113]. Notwithstanding this, MIA can lead to a disruption in immune tolerance, blood circulation, and cytoarchitecture of the placenta [160] and may alter the expression of genes that encode important fetal endocrine and growth factors, which are associated with schizophrenia and ASD [162].

Overall, although it can be possible all remodeling at the maternal-fetal interface (immune and hormonal changes) during pregnancy may be slightly protecting the offspring brain development against severe COVID-19 outcomes [163, 164], there is a large body of evidence, as discussed here, that support various conceivable ways by which SARS-CoV-2 infection could impair these protective maternal mechanisms (Fig. 1). However, further studies are needed to better understand how such mechanisms could be impaired by the SARS-CoV-2 infection.

Neuroimmune Disorders Associated with Maternal Infections

Immune and endocrine activation during pregnancy, as well as infections and stress, may influence fetal neurodevelopment and increase the risk of neurological and psychiatric diseases during postnatal life [165–176]. Stress conditions, such as anxiety and depression, are associated with a number of psychiatric disorders, such as ASD [177–179], depressive symptoms [180], anxiety,

Fig. 1. Hypothetical neuroimmune-endocrine mechanisms by which SARS-CoV-2 infection may lead to damages in fetal brain development. Under normal conditions, the maternal, fetal, and placental HPA axes work in an integrated manner to avoid damages to fetal neurodevelopment. During pregnancy, the levels of placental 11β -HSD2 (glucocorticoid-inactivating enzyme) rise throughout gestation, ensuring proper fetus exposure to glucocorticoids. Steroid hormones (e.g., progesterone) also increase during gestation progress, shifting the cytokine balance toward an anti-inflammatory profile at the maternal-fetal interface. During a viral infection (e.g., SARS-CoV-2 infection), such regulatory mechanisms could be impaired. In these circumstances, SARS-CoV-2 (1) may lead to a disruption in the suitable regulation of the HPA axis; (2) glucocorticoids controlling mechanisms, as placental 11β -HSD2 expression, may be disrupted and rise fetal exposure to these hormones, which could lead to neuropsychiatric disturbances in childhood or adulthood; (3) a dysregulation of progesterone production by the placenta can contribute to an unbalanced inflammatory environment for the fetus; and (4) the exacerbated maternal inflammation may break proper immune-endocrine interactions and impair the offspring's neurodevelopment (e.g., ASD-related cortical and behavioral abnormalities). SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; HPA, hypothalamic-pituitary-adrenal; CRH, corticotrophin-releasing hormone; 11β -HSD2, 11β -hydroxysteroid dehydrogenase type 2; ASD, autism spectrum disorders.



borderline personality disorder, eating disorders [181], ADHD [179, 182–184], and schizophrenia [185], which arise later in life.

SARS-CoV-2 infection is very recent; it is not yet possible to assess whether and what neurological consequences may occur in children born from mothers who had COVID-19. However, based on its clinical manifestations and making a parallel with other infections already described in the literature, attention is drawn to the risks represented by COVID-19 from a neurological point of view.

Fever was one of the most reported symptoms among both pregnant and nonpregnant patients infected with SARS-CoV-2. Fever during pregnancy can have different outcomes, depending on the cause (pneumonia, virus,

bacterial infections, malaria, genitourinary tract infections, etc.), temperature elevation, its duration, and the gestational period [186, 187]. Elevated body temperature of the pregnant woman can lead to events that compromise the development of the fetus such as vascular disruptions and placental infarction [187, 188]. Maternal fever during pregnancy has been associated with problems in fetal development as neural tube defects, congenital heart defects, oral clefts, growth retardation, abortions, and fetal death [186, 187, 189, 190]. The CNS is one of the most affected, leading to behavioral and cognitive problems that can develop during postnatal life [187] as an increased risk for development of ADHD [191] and autism [192–194].

Lymphopenia is frequently observed in COVID-19 patients. In fact, the lymphocyte count, as well as the neu-

Table 1. MIA can trigger neuropsychiatric outcomes in the offspring

Study reference	Women, N	Offspring, N (age)/ analysis method	Study population	Study design	Maternal inflammatory mediators (serum)	Potential causes of MIA	Gestational timing (for serum collection)	Offspring brain outcomes
102	N = 86	N = 43 controls N = 43 cases diagnosed with psychotic disorders (*)/ data of examination and interview	Adult	Case-control study cohort	<ul style="list-style-type: none"> ↑ IL-4 ↑ IL-5 ↑ IL-13 - IL-2 - IFN-γ - IL-12 - IL-6 - IL-1β - TNF-α 	Viral exposure (18.6%), hypoxia exposure (67.4%)	At the time of birth	Lower risk of developing psychosis
103	N = 164	N = 105 controls N = 59 cases diagnosed with schizophrenia spectrum disorders (14–38 years old)/Diagnostic Interview for Genetic Studies	Adult	Case-control study cohort	<ul style="list-style-type: none"> ↑ IL-8 - IL-1β - IL-6 - TNF-α 	N/D	Second and third trimesters	Higher risk of developing schizophrenia spectrum disorders
104	N = 246	N = 246 (4.5 years old)/ DAS-II and computer-based NIH toolbox	Children	Longitudinal study	<ul style="list-style-type: none"> ↑ IL-12p70 ↑ IL-17A ↑ IL-1β ↑ IFN-γ ↑ IL-8 - IL-4 - IL-6 - TNF-α 	Maternal smoking (19.1%); caesarian delivery (34.4%); gestational diabetes (6.7%); pre-pregnancy high BMI (28.7%)	First and second trimesters	Higher IL-12p70 and IL-17A were positively correlated with higher cognitive flexibility, inhibitory control, and attention. However, higher IL-1 β and IFN- γ were correlated with lower IQ score and a worse performance in cognitive flexibility task, respectively. Also, higher IL-8 was correlated with higher verbal abilities and lower spatial abilities
105	N = 156	N = 86 (4 weeks old)/sMRI N = 70 (4 weeks old)/fMRI N = 52/86 (24 months old)/sMRI N = 45/70 (24 months old)/fMRI	Newborn; infants	Longitudinal study	<ul style="list-style-type: none"> ↑ IL-6 	Overweight or obese (55.8%)	First, second, and third trimesters	Higher maternal IL-6 was associated with greater right amygdala volume, stronger left amygdala-fusiform and right amygdala-insula connectivity (at 4 weeks age), which were associated with lower impulse control (at 24 months age)
106	N = 147	N = 86 (0.7–8.2 weeks old)/MRI N = 30/86 (0.7–8.2 weeks old and 12 months old)/MRI and Social-Emotional Scale	Newborn; infants	Longitudinal study	<ul style="list-style-type: none"> ↑ IL-6 	N/D	First, second, and third trimesters	Higher IL-6 was associated with increased susceptibility for cognitive impairment (based on changes in frontolimbic circuitry at 12 months of age)
107	N = 72	N = 72 (6.5 weeks old)/MRI (14 months old)/BSID-III	Newborn; infants	Cross-sectional study	<ul style="list-style-type: none"> ↑ IL-6 ↑ CRP 	In part of mothers, higher and moderate IL-6 levels were correlated with caesarean section and spontaneous vaginal delivery, respectively	Third trimester	IL-6 increased: correlated with stronger left insula-mPFC and lateral-occipital gyrus connectivity. Also, weaker dACC and dmPFC connectivity CRP increased: correlated with greater connectivity between left insula and right temporoparietal junction, right insula and basal ganglia, dACC and cuneus, temporoparietal junction, and extrastriate cortex. Also, weaker connectivity between dACC and dmPFC and right basal ganglia MIA-related functional connectivity was localized to the salience, default mode, and frontoparietal networks, which have been implicated in the pathogenesis of psychiatric disorders

Table 1 (continued)

Study reference	Women, N	Offspring, N (age)/analysis method	Study population	Study design	Maternal inflammatory mediators (serum)	Potential causes of MIA	Gestational timing (for serum collection)	Offspring brain outcomes
134	N = 1,031	N = 428 controls N = 188 DD N = 415 ASD (subdivided into ASD + ID = 184 and ASD-noID = 201) (*)/DSM-IV	Children	Case-control study cohort	↑ GM-CSF ↑ IL-1α ↑ IL-6 ↑ IFN-γ ↑ IL-8 ↑ MCP-1 ↑ TNF-α ↑ IL-1β ↑ IL-10 ↑ IL-1Ra	N/D	Second trimester	GM-CSF, IL-1α, IL-6, IFN-γ were higher in ASD + ID compared to controls and indicated an increased risk. Higher IL-8 and MCP-1 were related to lower risk when compared between ASD-noID/DD and controls All increased inflammatory mediators indicated an increased risk when compared between ASD + ID and ASD-noID
137	N = 1,354	N = 677 controls N = 677 cases diagnosed with ASD (*)/ADI-R	Children	Case-control study cohort	↑ CRP	HIV, syphilis, and hepatitis	First and early second trimesters	Higher risk of developing ASD (43%)
138	N = 81	N = 54 controls N = 27 cases diagnosed with major psychotic disorder (13 with schizophrenia, 1 with schizophreniform disorder, 2 with bipolar disorder with psychotic features, 3 with brief psychosis, and 8 with psychosis not otherwise specified) (*)/DSM-IV, interview	Adults	Case-control study cohort	↑ TNF-α - IL-1β - IL-2 - IL-6 - IL-8	Maternal infections (16%)	At the time of birth	Higher levels of TNF-α during pregnancy were associated with increasing odds of psychosis in adult life
139	N = 25	N = 8 controls N = 17 cases (7 diagnosed with schizophrenia, 4 with schizoaffective disorder, and 6 with schizophrenia spectrum disorders) (39–40 years old)/MRI	Adult	Case-control study cohort	↑ IL-8	N/D	Second and third trimesters	Among cases, there were structural neuroanatomical alterations consistently related to schizophrenia spectrum disorders, such as an increase in ventricular cerebrospinal fluid, a decrease in left entorhinal cortex, and right posterior cingulate volumes
140	N = 292	N = 159 controls N = 84 ASD N = 49 DD (*)/DSM-IV	Children	Case-control study cohort	↑ IFN-γ ↑ IL-4 ↑ IL-5 ↑ IL-2 ↑ IL-6	N/D	Second trimester	IFN-γ, IL-4, and IL-5 were correlated with increased risk of developing ASD (50%). Also, IL-2, IL-4, and IL-6 were associated with increased risk of DD without autism
146	N = 150	N = 150 (1 month age)/paired-stimulus auditory paradigm N = 127/150 (3 months age)/IBQ-R indices – Surgency, Regulation, and Negativity	Newborn; Infants	Cross-sectional study	↑ CRP	Maternal infection, depression, obesity, and pre-pregnancy high BMI	Second trimester	CRP was associated with decreased cerebral inhibition in newborn males but not in females at 1 month age. At 3 months of age, cerebral inhibition was related to decreased infant regulation behaviors
148	N = 1,554	N = 777 controls N = 777 cases (630 diagnosed with schizophrenia and 174 with schizoaffective disorder) (*)/ICD-10	*	Case-control study cohort	↑ CRP	HIV, syphilis, and hepatitis	First and early second trimesters	High levels of maternal CRP were significantly associated with schizophrenia in offspring

(↑) increase; (–) no differences; (*) lack of data; N/D, not determined; MIA, maternal immune activation; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony stimulating factor; ASD, autism spectrum disorder; DD, developmental delay; ID, intellectual disability; IQ, intelligence quotient; ADI-R, Autism Diagnostic Interview-Revised; ICD, International Statistical Classification of Diseases and Related Health Problems; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition*; DAS-II, Differential Ability Scales – second edition; NIH, National Institutes of Health; BSID-III, Bayley Scales of Infant and Toddler Development – third edition; IBQ-R, Infant Behavior Questionnaire – Revised short form; MRI, magnetic resonance imaging; sMRI, structural magnetic resonance imaging; fMRI, functional magnetic resonance imaging; mPFC, medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; dACC, dorsal anterior cingulate cortex.

trophil count, has been associated with the severity of COVID-19 [118, 195, 196]. Some hypotheses have been raised to explain lymphopenia. (1) The death of lymphocytes could be a result of direct infection by SARS-CoV-2. (2) The drop in the number of lymphocytes could be a result of the damage caused by SARS-CoV-2 to organs such as the thymus and spleen. (3) The death of lymphocytes could be caused by the cytokine storm characteristic of some viral infections [197]. The latter has been widely reported in the literature [198–202] and can influence the fetal development in many ways as well as induce clinical manifestations that will only appear in postnatal life [55]. Neuropsychiatric and neurodevelopmental disturbances can be associated with MIA and have been widely reported in the literature, such as schizophrenia spectrum disorders, ASD, and ADHD (Table 1) [113, 173–175, 203–209].

Pregnant women with COVID-19 have elevated levels of CRP. CRP is used as a biomarker of systemic inflammation, even during pregnancy [210, 211]. Elevated CRP levels in the mid-term of pregnancy are correlated with late gestational complications [212], increased risk for preeclampsia [213], and increased risk of neonatal sepsis [214]. In addition to complications related to pregnancy itself, high levels of CRP can influence brain development [215] and are also related to psychiatric disorders such as schizophrenia [216, 217], autism [206], and bipolar disorder [218].

Another aspect that must be considered is the psychological stress caused by the COVID-19 pandemic in pregnant women. In addition to being more susceptible to infections, pregnant women during the pandemic have been commonly deprived of regular prenatal consultations. Social isolation, fear, insecurity, and lack of prenatal care contribute to maternal mortality and can interfere with fetal development [219]. An example of this is the increased risk of developing preeclampsia in women who experience depression or anxiety during pregnancy [220–222]. Vasoactive substances, hormones, and other neuroendocrine mediators have their excretion altered during depression, contributing to the increase in blood pressure, which, in turn, increases the risk of preeclampsia [221, 223].

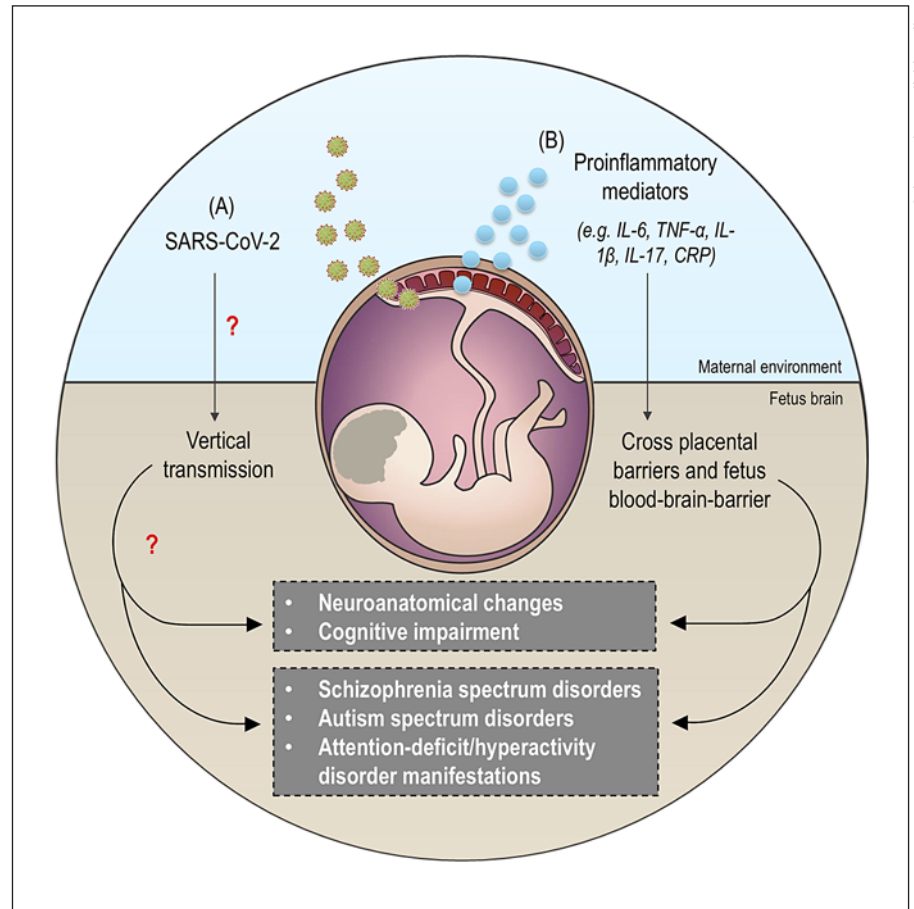
The literature has shown that SARS-CoV-2 has a correlation with hypertensive complications, such as preeclampsia [119, 126, 224–229]. Hosier et al. [126] demonstrated a case report in which a patient already had a history of gestational hypertension and had her condition aggravated after SARS-CoV-2 infection. The patient was in the second gestational trimester and, until then, had no

indication of gestational hypertension. After infection, her clinical and laboratory tests showed hypertension, proteinuria, elevated transaminases, and low platelet counts, indicating a diagnosis of severe preeclampsia. The examination of the placenta showed inflammation, with inflammatory infiltrates composed of macrophages and T lymphocytes, in addition to the virus in the syncytiotrophoblast cells, which suggests that COVID-19 is related to placental inflammation, which may favor the appearance of preeclampsia [126]. Other evidence shows that SARS-CoV-2 promotes lesions in the placenta that increase decidual arteriopathy and maternal vascular malperfusion, findings that are compatible with hypertensive disorders and preeclampsia [230]. It is worth mentioning that preeclampsia is mostly observed in the severe forms of COVID-19 [226] and pregnant women who have a history of hypertensive disorders of pregnancy [126, 231, 232].

To date, most evidence indicate that vertical transmission of SARS-CoV-2 from mother to fetus does not occur [120, 233, 234]. Only 2 reports indicate that vertical transmission could occur [235, 236]. However, even if there is no vertical transmission, this does not exclude dangers for fetal development. The maternal immune system, although naturally altered due to the peculiarities of pregnancy, has mechanisms to fight pathogens. Some adaptive immune responses are downregulated during pregnancy as decreased numbers of T and B cells. On the other hand, NK cells and monocytes respond strongly to viral challenges, producing inflammatory mediators [237]. Thus, even if the virus is not able to cross the placenta and reach the fetus, several complications can occur because of the maternal inflammatory response to the virus. Cytokines and hormones of maternal origin can freely cross the placenta, a phenomenon called “vertical transfer” [99].

Thus, it can be said that the impact that the infection will have on fetal development will depend on a set of factors, such as the trimester of pregnancy and the location of the pathogen (whether they are present in the maternal-fetal interface or only in maternal tissues) in addition to the maternal-placental immune response [55]. Based on the data available in the literature, COVID-19 in pregnant women presents itself mostly in mild forms, with most fetuses born alive. Thus, since mothers are subjected to an exaggerated inflammatory response, attention is drawn to possible consequences for neurodevelopment as well as neural and psychiatric diseases that may arise in postnatal life (Fig. 2).

Fig. 2. Major pathways for neurodevelopmental and neuropsychiatric outcomes in the offspring of mothers infected by SARS-CoV-2. SARS-CoV-2 infection during pregnancy could lead to devastating outcomes in the offspring's brain, and in this case, there are 2 major pathways that can be responsible for affecting brain health and its proper development. **a** First, the virus could supposedly cross placental tissues (vertical transmission) and reach the fetus' brain, leading to harmful effects. **b** Second, despite the SARS-CoV-2 vertical transmission possibility, the virus can trigger an exacerbated inflammatory response in the infected pregnant mother (upper panel). The inflammatory mediators produced by the mother can effectively cross all placental barriers and the fetus' BBB, which can trigger neurodevelopmental and/or neuropsychiatric damages in the offspring (e.g., neuroanatomical changes, cognitive impairments, schizophrenia spectrum disorders, ASD, and ADHD manifestations) (bottom panel). SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; BBB, blood-brain barrier; ASD, autism spectrum disorders; ADHD, attention-deficit/hyperactivity disorder.



The Risk of Fetal and Neonatal SARS-CoV-2 Infection

The clinical manifestations of COVID-19 in pregnant women appear to remain the same as in nonpregnant patients. It is of great importance whether the new coronavirus can be transmitted vertically from the pregnant woman to the fetus. The youngest baby tested positive for SARS-CoV-2 was 36 h old [235].

In the SARS-CoV pandemic that occurred in 2002–2003, from 12 pregnant women infected, 3 died, 4 miscarried in the first trimester, and 4 gave birth prematurely [112]. In the MERS-CoV infection, from 11 women infected, 3 died in the second trimester of pregnancy, 6 patients required hospitalization in the intensive care unit, and only 2 neonates died [238].

Although the question of SARS-CoV-2 transplacental infection (vertical transmission) has not been conclusively answered, reports of neonatal infection with COVID 19 shortly after delivery suggest transplacental migration or horizontal transmission by direct contact with the sur-

face at birth or during breastfeeding as the mode of viral migration [239]. Transplacental migration is different from the direct or “mechanical” transfer of viruses, as they can occur in prenatal procedures such as amniocentesis, premature birth, and hemorrhage [240].

Clinical evidence of transplacental viral migration requires the isolation of viral nucleic acids in fetal or placental tissues in the sterile intrauterine environment and/or in the newborn as well as the adequate exclusion of horizontal transmission, such as direct or mechanical transfer of virions or contamination through the genital tract fluids during vaginal delivery. It is necessary that the diagnostic tests include an adequate range of biological samples from the mother and the newborn, such as amniotic fluid, umbilical cord blood, vaginal secretions, placenta, and neonatal nasopharyngeal swabs. PCR is the method of choice to isolate SARS-CoV-2 nucleic acids [241].

Maternal SARS-CoV-2 infection in the first and second trimesters of pregnancy increases the risk of early

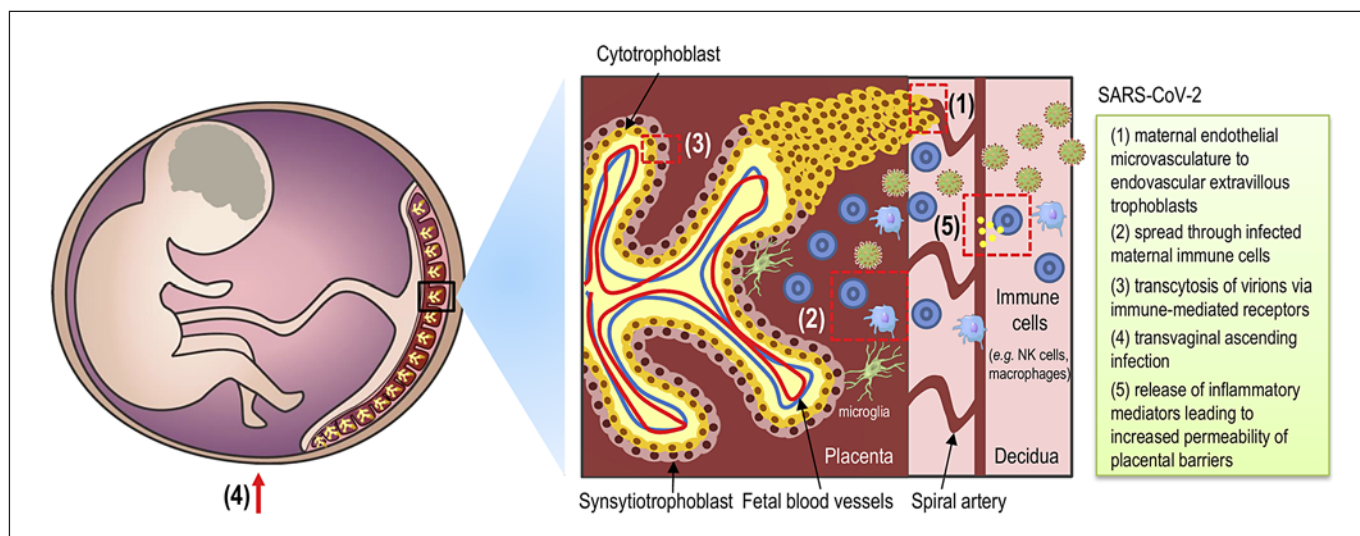


Fig. 3. Possible pathways for SARS-CoV-2 vertical transmission at the maternal-fetal interface. Similar to other pathogens, SARS-CoV-2 infection during pregnancy could reach the placenta and impair the fetal development through different pathways. This schematic picture shows the fetus inside the intrauterine cavity (left panel), along with a magnification of the maternal-fetal interface with its main components such as placenta, decidua, spiral artery, fetal blood vessels, trophoblast cells (e.g., cytotrophoblast and syncytiotrophoblast), immune cells (e.g., NK cells and macrophages), and migrating microglia (middle panel). There are some

possible pathways for SARS-CoV-2 vertical transmission crossing the maternal-fetal interface and were indicated by the numbers throughout the picture (dashed red square) and in the right panel: (1) through maternal endothelial microvasculature to endovascular extravillous trophoblasts; (2) spread through infected maternal immune cells; (3) transcytosis of virions via immune-mediated receptors; (4) transvaginal ascending infection; and (5) release of inflammatory mediators leading to increased permeability of placental barriers. SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; NK, natural killer.

miscarriage, fetal death in utero, and growth retardation. A study published in 2004 during the SARS epidemic found a higher rate of miscarriage, premature delivery, and stunting but no evidence for vertical transmission of SARS-CoV-1 [112]. In addition, abnormally high mortality was not observed in pregnant women infected with SARS-CoV-2 compared to what had been observed during the epidemics of SARS-CoV-1 and MERS-CoV [242]. For the moment, no fetopathy has been described in fetuses or neonates whose mothers had COVID-19 [243].

During primary infections, virus circulation in the bloodstream, even for a short time, is an essential factor for its transplacental transport and maternal-fetal transmission through viral tropism toward the placenta [243]. Indeed, such a mechanism could be applied for the possible vertical transmission of SARS-CoV-2. The possible placental crossing by SARS-CoV-2 is similar to other pathogens, and the route for vertical transmission could occur by 5 typical pathways: (1) the maternal endothelial microvasculature to endovascular extravillous trophoblasts; (2) spreading through infected maternal im-

mune cells; (3) transcytosis of virions via immune-mediated receptors; (4) transvaginal ascending infection; and (5) release of inflammatory mediators leading to increased permeability of placental barriers (Fig. 3) [244, 245].

Studies with placentas delivered from mothers with COVID-19 evaluated the presence of SARS-CoV-2 for RT-PCR but found no evidence for the virus. Histopathological analysis performed in 3 placentas also did not reveal tissue alterations [139, 235, 246–248]. To confirm vertical transmission, it has been proposed that detection of the virus by PCR in umbilical cord blood, neonatal blood collected within the first 12 h of birth, or amniotic fluid collected prior to rupture of membranes is needed [241, 249]. It is important to note that ACE2, the receptor for SARS-CoV-2, is present only at very low levels in the human placenta during the first trimester of pregnancy [250], while there are no data on the expression of this receptor in second and third trimester placentas [243].

Apparently, vertical transmission of SARS-CoV-2 is not frequent, although it cannot be, yet, completely dis-

missed. Reports of neonatal infection with COVID-19 shortly after delivery suggest either transplacental migration or horizontal transmission through contact with maternal mucosa at delivery or during breastfeeding as the mode of viral migration [14, 239].

Another possibility for the virus to cross the placental barrier is to be carried by an infected blood cell. However, SARS-CoV-2, if able to enter into peripheral blood mononuclear cells, does not seem to replicate in these cells, such as SARS-CoV [243, 251]. Additionally, the resident macrophages of the lymph nodes express the ACE2 receptor, and in terminally ill patients, the virus is found in these cells but not in T or B lymphocytes [235, 252]. SARS-CoV-1, which also uses the ACE2 receptor, is also found in alveolar macrophages [253]. Although no replication or transport of infectious viruses by macrophage monocytes has been demonstrated, lymph node and spleen macrophages can harbor the virus [243].

Maternal-Fetal Interface and the Harmful Effects of SARS-CoV-2 Infection on the Fetus

Viruses replicate in various cell types within the maternal-fetal interface. In the case of ZIKV, evidence of viral replication was identified in proliferating villus and Hofbauer cells (fetal macrophages) in the villous core [254]. Additionally, the ability of ZIKV to be transmitted sexually allows it to bypass the trophoblast layer via ascending infection of the amniochorionic membrane [255].

Findings reported by Jain et al. [256] have described 2 neonates born from SARS-CoV-2-positive women with diverse manifestations. They observed that neither infant was positive for SARS-CoV-2 infection by RT-PCR [256]. These findings are similar to a previous study that demonstrated that out of 33 neonates born from women with SARS-CoV-2 infection, only 3 were found to be positive by RT-PCR at varied time periods after birth [257]. In another study case, 7 neonates born from SARS-CoV-2-infected women were found to be negative with diverse manifestations, including premature birth, fetal distress, and neonatal respiratory distress syndrome [258, 259].

A study by Egloff and colleagues [243] reported that patients were infected in late pregnancy and give birth a few days after infection. Regarding time, the mean gestational age was 37 weeks and 1 day, and the range was 30–40 weeks and 2 days. Of 81 (69%) newborns who were tested for SARS-CoV-2, 5 (6%) had a positive result [236, 260]. Tests were performed more frequently with nasopharyngeal swabs in 46 neonates (57%), followed by 16

breast milk (20%) and throat swabs in 10 neonates (12%) [261]. The tests were repeated; of 79 neonates, 49 (62%) were subjected to a new test, and all neonates except 1 subsequently tested negative for SARS-CoV-2 [261]. Premature birth, defined as a gestational age of <37 weeks, was observed in 24 (20%) newborns. In 47 neonates whose information on birth weight was disclosed, 42 (89%) had adequate weight for their gestational age (AGA). Three (7%) newborns were underweight for the gestational age (SGA), and 2 (4%) newborns were overweight for their gestational age (SGA). In another study, 9 neonates (5%) had respiratory dissipation or shortness of breath, depending on the complications. There has been 1% neonatal death [138]. A study carried out by Thomas et al. in 2020 observed that the newborn's mother had complications such as vaginal bleeding in the third trimester and a positive test for SARS-CoV-2 three days after cesarean delivery, when she first presented with symptoms of COVID-19 (fever). In the study, the newborn who died had a negative result for SARS-CoV-2 [261].

Walker et al. [249] stated that COVID-19 disease should not be an indication for cesarean delivery, differentiated feeding, or isolation of the mother's baby. C-sections should continue to be performed for normal obstetric indications. Mothers who breastfeed and stay with their babies should continue to observe COVID-19 hygiene precautions. There are many evidence supporting isolation between newborn and mother, in detriment of the beneficial contact of them [249].

Conclusion

Pregnancy may be a risk factor for respiratory virus infections. For example, during the H1N1 epidemic in 2009, it was observed that pregnant women had a higher risk of complications, as they were 4 times more likely to be hospitalized than the rest of the population [262]. Pneumonia is one of the most prevalent non-obstetric infections in pregnant women, being one of the most common causes of maternal death. It also requires ventilatory support in 25% of cases [263–265]. During pregnancy, morbidity and mortality from viral pneumonia are more serious than bacterial pneumonia, frequently causing premature rupture of membranes, stillbirth, intrauterine growth restriction, and premature birth [263].

So far, this does not seem to be the case for the current SARS-CoV-2 pandemic. In contrast, there is no evidence showing significant differences in the pathophysiology or

severity of the disease between pregnant and nonpregnant women. In fact, pregnant women generally showed mild to moderate degrees of infection, with most babies being born alive. This scenario calls attention to possible neurological consequences that can arise to babies who have been subject to an exacerbated maternal immune response to fight the virus.

The placenta is a physical and immunological defense against fetal infection. Maternal NK cells, deciduous macrophages, and T cells surround the placenta. Immune cells are vital in the remodeling and implantation of the placenta; deficiencies are associated with spontaneous abortion and other adverse pregnancy outcomes [266]. Although evidence shows that vertical transmission does not occur, infection by SARS-CoV-2 disturbs the maternal-fetal interface, changing immune cells signaling present there. This in turn leads to an increase in inflammatory cytokines that cross the placenta and can influence the neurodevelopment of the fetus. Therefore, it is important to evaluate and monitor these babies to assess whether COVID may induce neurological sequelae or psychiatric disease in the future.

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Statement of Ethics

The article is exempt from approval by the Ethics Committee because it is a review article.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.G.G. and A.C.R.O. designed the study. M.G.G., A.C.R.O., A.P.G., and E.C.F. performed the bibliographic search and wrote the manuscript. C.S.F. prepared the figures, table, and wrote the manuscript. E.G.-A. and H.C.C.-F.-N. reviewed the manuscript. All authors have approved the final manuscript.

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