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COVID-19 in pregnancy – a possible risk factor for the poor neurological outcome of the infant

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INTRODUCTION

The medical literature indicates that congenital viral infections can generate neurological disorders [1,2]. Disorders that manifest as a reduction in fetal movements have been observed in combination with irritability, ineffective sucking, axial hypertonia or hypotonia and opisthotonos in newborns exposed to SARS-CoV-2 in intrauterine life [3,4]. There are also studies in which newborns prenatally exposed to SARS-CoV-2 did not develop neurological changes [5]. To date, scientific evidence is conflicting and no clear patterns have been found to explain the broad spectrum of effects of SARS-CoV-2 on the central nervous system (CNS) in the newborn. As with SARS-CoV and MERS, the long-term impact on brain development is not precisely known [6,7]. Obvious clinical manifestations may not appear from the first weeks of life [8]. To fully understand neurodevelopment, multiple neurodevelopmental assessments and electrophysiology studies such as auditory evoked potentials are needed [9].

The best indicator for the evaluation of general motor skills is agitation movements, as their absence has been shown to have a high predictive value regarding the occurrence of adverse neurological outcomes, such as cerebral palsy, with a specificity and sensitivity of 89% and 97% respectively [10,11,12]. The high predictive power is probably due to the fact that these movements are conclusive in terms of the ontogeny of general movements and the involvement of multiple areas in the brain, not only areas involved in motor control but also neighboring areas involved in emotional and cognitive control [13,14].

The relationship between maternal infection with COVID-19 to the neurodevelopment of the newborn is not yet fully understood. However, the profound immune activation observed in a subset of infected individuals suggests that the developing fetal brain may be influenced by maternal and placental inflammation and altered cytokine expression during key periods of development [15,16,17]. Regardless of the mechanism, epidemiological studies demonstrate that maternal infection in pregnancy with SARS-CoV-2, including other viral infections such as influenza, is associated with adverse neurodevelopmental outcomes in the offspring, including autism spectrum disorders, paralysis cerebral palsy, schizophrenia, bipolar disorder, cognitive dysfunction, anxiety and depression [18,19,20]. Although the magnitude of these effects and the percentages in which they correlate vary, the consistency of such associations is hard to ignore [21].

VERTICAL TRANSMISSION OF SARS-COV-2 DURING PREGNANCY

The likelihood of newborns acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from infected mothers has sparked intense debate in the medical world. Published studies have reported wide variability in the rate of vertical transmission.

With the spread of COVID-19, pregnant women are at greater risk, as they have a worse prognosis than non-pregnant women in case of SARS-CoV-2 infection. Further studies with a large sample size are needed to confirm the percentage of vertical transmission of the infection [22].

Changes in maternal cardiovascular and respiratory systems, including increased heart rate, oxygen consumption, decreased lung capacity, as well as im-

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munological changes that allow a mother to tolerate an antigenically distinctive fetus, increase the risk for pregnant women to develop severe forms of respiratory disease [23]. Data from several influenza control studies have demonstrated an increased risk of maternal morbidity and mortality compared to non-pregnant women. The same association was highlighted for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) infections [24].

Current evidence shows that the risk of vertical transmission of SARS-CoV-2 is low (approximately 3%). Laboratory tests revealed the presence of SARS CoV-2 in the amniotic fluid and on the fetal part of the placenta [25,26]. On the placenta, the expression of angiotensin-converting enzyme-2 (ACE2) acts as a receptor for the entry of SARS-CoV-2 into cells [27]. In addition, vertical transmission can occur during vaginal birth through contact with the virus present in the mother's stool [28,29].

Fetal infection, due to direct access of the virus from the maternal bloodstream to the amniotic fluid and then to the fetal cells, has different rates depending on the state of the host's immune system, pathogen characteristics, gestational age and virulence; however, vertical transmission is not the only way viruses can affect the fetal central nervous system (CNS). How SARS-CoV-2 enters cells is widely known and involves the transmembrane serine protease-supported angiotensin-converting enzyme-2 (ACE2) 2 (TMPRSS2), which promotes the fusion of the viral capsid with the host cell [30,31].

Several human tissues express ACE2, including placental syncytiotrophoblast cells, and histological analysis of SARS-CoV-2-infected placentas showed direct and indirect evidence of infection, with placental lesions and signs of malperfusion and inflammation [32].

This evidence of tissue changes suggests a weakening of the placental barrier with a higher risk of vertical transmission; however, recent studies have demonstrated limited expression of SARS-CoV-2 ex vivo in the placenta under acute infection and inefficient replication of placental SARS-CoV-2 in vitro in different types of placental tissues [33]. Moreover, ACE2 expression has been shown to be lower between 6 and 14 weeks of gestation, increasing at the end of pregnancy, when organogenesis is already completed, and co-expression of ACE-2 and TMPRSS2 is undetectable in placental cells throughout pregnancy, reducing the risk of direct effects on the fetal CNS. In a recent systematic review of the literature, no cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to fetuses were proven, confirming a very low rate of vertical transmission [34,35]. In fact, SARS-CoV-2 has been reported in the placentas of women severely affected by COVID-19, suggesting that in asymptomatic and mildly symptomatic patients, the placental barrier maintains its integrity and function [36].

THE MECHANISM OF FETAL BRAIN DAMAGE

Maternal cytokine-associated inflammatory response during pregnancy has previously been studied in the literature as a link between viral infection and fetal brain injury [37]. Cytokines may originate from the maternal peripheral immune system and reach the fetal bloodstream by crossing the placenta or may arise through placental or fetal production [38]. It has been shown that fetal glial cells can also produce cytokines after an inflammatory stimulus, and it has been suggested that microglia can act as a promoter of oligodendrocytes and neuronal damage by producing cytokines [39].

IL6, TNF, IL8 and IL1 are the main cytokines involved in fetal brain injury. It is quite interesting that these same cytokines are also involved in fetal inflammatory response syndrome (FIRS) secondary to intrauterine infections, which leads to preterm premature rupture of membranes and preterm birth. Studies have shown that FIRS, and not prematurity, appears to be involved in periventricular hemorrhage, leukomalacia (PVL), and cerebral palsy in preterm infants [40]. A recent study demonstrated that fetal gender can influence the mother's ability to counteract an inflammatory response: pregnancy with a male fetus showed higher levels of IL1 and greater nitrosative injury in the presence of an oxidative environment, with a higher risk of damage to the fetal brain [41].

The mechanism behind fetal brain injury appears to involve direct cytokine injury to oligodendrocytes and neurons and secondary injury through the activation of microglia and astrocytes with the release of free radicals, cytotoxic cytokines, and excitotoxic metabolites. It has been demonstrated that TNF decreases the number of progenitor oligodendrocytes through apoptosis and inhibition of their differentiation. This inflammatory environment can produce neuronal disorders, with axonal loss, neuronal death, cytoskeletal damage and disruption of neuronal migration from the ventricular zone to the neocortex, with abnormal cortical development [36,42].

The biological basis or mechanism by which maternal psychological stress associated with pandemic events would be an important neurodevelopmental factor alongside maternal viral infections during pregnancy remains unclear, and this putative association requires validation in larger, longer-term studies [21].

SHORT TERM RESULT

Maciel de Moraes and co. published in 2022 a literature review regarding the effects of pregnancy

COVID-19 infection on newborns. They observed that about a quarter of newborns come from mothers who were infected with SARS-COV-2 in pregnancy asymptomatic [43].

The coronavirus has been detected in cerebrospinal fluid (CSF), which suggests that once it reaches the lungs, it spreads throughout the body, eventually reaching the central nervous system (CNS) [44]. Coronaviruses have the potential to cause neurological damage through various pathways. CNS tropism of the virus can lead to serious sequelae, including encephalitis, toxic encephalopathy, and severe acute demyelination [44]. Neurological changes were observed in 26.44% of neonates, with lethargy being the most common symptom (9.20%). Irritability, hypotonia, apnea crises, and convulsions were also mentioned, in varying percentages. Cough, tachypnea, coryza, and respiratory distress were observed in neonates with respiratory symptoms. About a quarter of the newborns were febrile. Vomiting, feeding intolerance, and abdominal distension were among the gastrointestinal manifestations, present in 21.84% of neonates. The most common gastrointestinal symptom was feeding intolerance (18.39%). Cardiovascular features were tachycardia and hypotension, which were present in 4.60% of infants [43].

LONG-TERM RESULT

In the detailed assessment of the motor repertoire, it is important to assess not only the general movements but also the movement and postures that are evident at 3-5 months. Only atypical body symmetry was consistently present and significantly different between the SARS-CoV-2-exposed and unexposed groups. Normally, restless movements and symmetrical body posture improve head control, which in turn allows the child to better interact with the environment, which could create a better foundation for both psychomotor development and positive engagement during interaction with parents. Body asymmetry and posture characteristics should be considered during the assessment and timely intervention to improve early neurodevelopment in infants prenatally exposed to SARS-CoV-2 [14].

Apart from organic brain damage, intrapartum or early-life infections are known to be associated with a wide spectrum of cognitive deficits and neuropsychiatric disorders. Depression and bipolar disorder have been associated with intrauterine viral infections. Schizophrenia and autism seem to be influenced by genetics and environmental factors, and maternal infections in pregnancy. It has been suggested that the inflammatory environment may act by different mechanisms, such as functional reprogramming of innate immune cells in the fetal brain, epigenetic changes in brain development genes, and permanent impairments of synaptic pruning. In a recent literature review, Figueiredo et al. warned of the potential role of SARS-CoV-2 in triggering autism and schizophrenia in the offspring of affected mothers [36,45].

PREVENTION OF A NEGATIVE FETAL OUTCOME OF SARS-COV-2 INFECTION

A healthy lifestyle and moderate physical activity have been shown to be effective in the prevention of excessive weight gain and the occurrence of diseases in pregnancy, such as gestational diabetes. In fact, gestational diabetes is linked to an increased susceptibility to viral infections, severe disease and associated complications, while obesity is a negative prognostic risk factor in patients affected by COVID-19, especially in the case of concomitant malnutrition or deficiency of trace elements.

A healthy maternal diet should include vegetables, fruits, olive oil, nuts, fish, essential and polyunsaturated fatty acids, and fiber-rich carbohydrates. In addition, minerals and vitamins are mostly supplemented to support physiological gestation and immune system activity.

In this context of high energy consumption, viral infection represents additional stress that results in more increased energy consumption and an intense immune system response that requires additional energy input; in addition, diet is one of the most important factors influencing the immune system.

Individual prevention measures such as self-isolation, physical distancing and sanitation are fundamental in association with vaccines in preventing transmission and are included in all guidelines of public health strategies [36].

DISCUSSION

Intrauterine transmission is one of the most serious complications of viral diseases that occur during pregnancy. Infectious agents can be transmitted vertically as in the case of the TORCH complex (Toxoplasma, others, rubella, cytomegalovirus, herpes). The same happens with the Zika virus and the Ebola virus. Maternal-fetal transmission of viral infections (except herpes virus) is usually by the hematogenous route in which the virus circulating in maternal blood enters the placenta, reaches the chorionic villus tree and fetal blood vessels, and is transmitted to the fetus. Fortunately, it has been shown that this mechanism of transmission does not occur when pregnant women are infected with the pathogenic coronaviruses - SARS-CoV and MERS-CoV - although clinical infections caused by these coronaviruses have resulted in severe maternal pneumonia, maternal deaths and early losses of the pregnancy.

The identification of newborns at risk of neurological disorders is necessary for timely intervention in the case of all those exposed to SARS-CoV-2 infection during pregnancy.

Follow-up programs should be implemented to reduce the consequences of in-utero exposure to SARS-CoV-2 because infants prenatally exposed to SARS-CoV-2 may develop a wide spectrum of neurological disorders [24].

CONCLUSION

As this pandemic continues, more information will become available about the effects of COVID-19 on pregnant women and their babies. Continued vigilance is required, as infection with COVID-19 can cause serious complications in the newborn. The newborn requires continuous clinical monitoring and, most importantly, to be protected from the horizontal transmission.

Because the inflammatory activity proved to be predominant in the case of maternal COVID-19 with a possible indirect effect on fetal cells, including cells of the central nervous system, supplementation with nutrients and antioxidants can be helpful in counteracting the negative effects of SARS-CoV-2 infection in pregnancy.

Fetal brain injury during SARS-CoV-2 infection appears to be mediated by the maternal immune response and the subsequent release of pro-oxidant products and cytokines, which interfere with normal neurological development and neuronal migration. A diet rich in antioxidant and anti-inflammatory micronutrients can mitigate the negative effects of inflammation on the fetal brain. In particular, arginine, n-3 PUFA, vitamins B1 and B9, choline and flavonoids have shown a beneficial effect in vivo and in vitro in reducing cellular damage during and outside pregnancy and may be considered in pregnant patients infected with COVID-19.

Future studies from larger and more diverse populations are needed to provide a more accurate estimate of the incidence of early-onset neonatal COVID-19 infection.

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