REVISTA NEUROCIÊNCIAS

Revisão

Possível risco de desenvolvimento fetal de autismo em gestantes infectadas por SARS-CoV-2

Possible risk of fetal development of autism in pregnant women infected by SARS-CoV-2

Posible riesgo de desarrollo fetal de autismo en mujeres embarazadas infectadas con SARS-CoV-2

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Resumo

Introdução. Em março de 2020, a Organização Mundial da Saúde (OMS) anunciou o surgimento de uma pandemia global, a COVID-19. Uma doença deflagrada pela infecção do novo coronavírus (SARS-CoV-2). Achados recentes indicam que o período gestacional pode tornar a mãe e sua prole mais suscetíveis ao novo coronavírus, com rápida progressão para o estágio crítico da doença. O organismo materno apresenta certo grau de deficiência imunológica e cardiorrespiratória, devido às adaptações fisiológicas ao período gestacional e, consequentemente, se acometido por infecções pré-natais causadas por vírus, levam à Ativação Imune Materna (AIM) exacerbada, contribuindo, assim, para alterações na neurogênese materno-fetal, na mielinização fetal, estando diretamente envolvida na patogênese de transtornos do neurodesenvolvimento na descendência. **Objetivo.** Este estudo traz como hipótese a possibilidade de infecções maternas por COVID-19 durante a gravidez ser um risco potencial para a prole desenvolver o Transtorno do Espectro Autista (TEA). **Conclusão.** Durante o período gestacional, as exposições a agentes infecciosos virais levam à Ativação Imune Materna exacerbada, contribuindo para alterações na neurogênese materno-fetal. Infecções pelos SARS-CoV-2 podem estar envolvidas na patogênese de transtornos do neurodesenvolvimento, como o TEA. Logo, uma atenção maior deve ser dada à prole de mulheres grávidas com COVID-19, uma vez que processos infecciosos pré-natais têm forte correlação com a prevalência de encefalopatias adquiridas.
Unitermos. Período Gestacional; SARS-CoV-2; COVID-19; Transtorno do Espectro Autista; Fator de Risco; Risco Fetal

Abstract

Introduction. In March 2020, the World Health Organization (WHO) announced the emergence of a global pandemic, COVID-19. A disease triggered by the new coronavirus infection (SARS-CoV-2). More recent findings indicate that the gestational period makes the mother and her offspring more susceptible to the new coronavirus and the rapid progression to the critical stage of the disease. The maternal organism presents a certain degree of immunological and cardiorespiratory deficiency due to physiological adaptations to the gestational period and, consequently, if affected by prenatal infections caused by viruses, they lead to an exacerbated Maternal Immune Activation (MIA), thus contributing to alterations in maternal-fetal neurogenesis, fetal myelinization, and is directly involved in the pathogenesis of neurodevelopmental disorders in the offspring, especially autism. **Objective.** This study hypothesizes that maternal COVID-19 infections during pregnancy are a potential risk for the

offspring to develop Autism Spectrum Disorder. **Conclusion.** The exposure to viral infectious agents during the gestational period leads to exacerbated maternal immune activation. It contributes to alterations in maternal-fetal neurogenesis and is directly involved in the pathogenesis of neurodevelopmental disorders, being correlated to the predisposition to affective and psychiatric disorders in the offspring. Therefore, greater attention should be given to the offspring of pregnant women infected by COVID-19, since prenatal infectious processes have a strong correlation with the prevalence of Autistic Spectrum Disorder in the offspring.
Keywords. Gestational period; SARS-CoV-2; COVID-19; Autism Spectrum Disorder; Risk Factor; Fetal Risk

Resumen

Introducción. En marzo de 2020, la Organización Mundial de la Salud (OMS) anunció la aparición de una pandemia mundial, COVID-19. Enfermedad provocada por la infección del nuevo coronavirus (SARS-CoV-2). Los hallazgos más recientes indican que el período gestacional hace que la madre y su descendencia sean más susceptibles al nuevo coronavirus y la rápida progresión a la etapa crítica de la enfermedad. El organismo materno tiene un cierto grado de deficiencia inmunológica y cardiorrespiratoria, debido a adaptaciones fisiológicas al período gestacional y, en consecuencia, si se ve afectado por infecciones prenatales causadas por virus, conduce a una Activación Inmunológica Materna (AIM) exacerbada, contribuyendo así a alteraciones. en la neurogénesis materno-fetal, en la mielinización fetal y está directamente involucrado en la patogénesis de los trastornos del neurodesarrollo en la descendencia, especialmente el autismo. **Objetivo.** Este estudio plantea la hipótesis de la posibilidad de que las infecciones maternas por COVID-19 durante el embarazo sean un riesgo potencial para que la descendencia desarrolle un trastorno del espectro autista. **Conclusión.** Durante el embarazo, la exposición a agentes infecciosos virales conduce a una activación inmunitaria materna exacerbada. Por tanto, contribuye a los cambios en la neurogénesis materno-fetal y está directamente involucrado en la patogénesis de los trastornos del neurodesarrollo. Por lo tanto, se debe prestar más atención a la descendencia de mujeres embarazadas infectadas con COVID-19, ya que los procesos infecciosos prenatales tienen una fuerte correlación con la prevalencia del trastorno del espectro autista en la descendencia.
Palabras clave. Período gestacional; SARS-CoV-2; COVID-19; Desorden del espectro autista; Factor de riesgo; Riesgo Fetal

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INTRODUCTION

In March 2020, the World Health Organization (WHO) announced the emergence of a global pandemic, COVID-19, for *Coronavirus Disease* 2019. A disease triggered by the new coronavirus infection (SARS-CoV-2), which causes acute respiratory syndrome; it can manifest mildly, evolving in some cases to a severe and rapid type of pneumonia with respiratory failure, progressing to death[1].

It was first detected in December 2019 in Wuhan, China, quickly spreading throughout Chinese territory and in several countries. The new member of the coronavirus family, SARS-CoV-2, was classified, due to its pathophysiology, similar to the other epidemics already known; Respiratory Syndrome (MERS), caused by the MERS-CoV virus and Severe Acute Respiratory Syndrome (SARS), coming from SARS-CoV, being now the seventh member of this class of viruses that infect humans[1].

Therefore, studies began to classify possible conditions as risk factors for more serious outcomes of the disease, such as individuals 65 years of age or older, people of any age with severe obesity (BMI>40), asthmatics, heart disease, hypertensive and diabetics[2].

Research published at the beginning of the pandemic indicated that pregnant women did not appear to be at risk of developing serious symptoms of the disease more than the population outside risk groups. However, more recent findings indicate that the gestational and postpartum periods make mothers and their offspring more susceptible to the new coronavirus and the rapid progression to the critical stage of the disease[3]. Pregnancy increases the risk of obstetric and neonatal adverse outcomes of several respiratory viral infections. Physiological and immunological alterations occur as a normal component in the gestational period, and systemic alterations can occur in the maternal organism that increase the danger of severe respiratory complications[2].

It is known that other diseases such as swine flu, Influenza A (H1N1), as well as those coming from the coronavirus family, such as SARS, MERS, can affect pregnancy, bringing damage to fetal development and increasing maternal and perinatal morbidity and mortality[1]. Such complications can be a warning sign for fetal health. Episodes that occur when the fetus is still in the maternal uterus, such as maternal infections by different pathological agents are correlated with future mental disorders in the offspring. Autism Spectrum Disorder (ASD) was correlated with hospitalizations for viral infections in individuals who were in their first trimester of pregnancy[4].

Autism Spectrum Disorder (ASD) is a severe neuropsychiatric disorder, defined by a set of clinical manifestations that include changes in the ability to communicate and interact with each other, in addition to stereotyped and repetitive behavioral patterns, with at least one of these manifestations evidenced during early childhood and extending through life, varying semiologically with age. The ASD is more frequent among men than women (proportion 4:1)[4].

The prevalence of ASD 15 years ago was 1:10,000[5]; however, in more recent studies, the prevalence of ASD is 1:54 in the United States (USA) and 1:160 worldwide[6]. These statistical differences are since the *Centers for Disease Control and Prevention* (CDC/USA) has been tracking the number and characteristics of children on the autism spectrum for over two decades, with prevalence information

on ASD updated and released every 2 years. However, the scarcity of data in several countries around the world, especially in less developed regions, changes in diagnostic criteria, methodology used, date of data collection, and differences in sample sizes suggest the impossibility of adequately estimating the global prevalence of autism[6].

ASD is considered a challenging public health problem because it has a high prevalence, resulting in increased responsibility for health care networks, producing high costs to the public and private system, as well as to society[5].

In the current pandemic scenario, as the number of confirmed COVID-19 cases in the world increases dramatically, evidence on the transmission, incidence, and effects of SARS-CoV-2 infection in mothers and their offspring remains limited. This is since COVID-19 is a new pathology, corroborating the lack of available data about this disease. However, some countries have carried out epidemiological research evidencing a gradual increase of contamination by COVID-19 in this population, suggesting a high number of pregnant women affected by coronaviruses (SARS-CoV-2) in a short period of time[7].

Thus, the maternal organism that already presents with a certain degree of immune deficiency due to physiological adaptations to the gestational period and, consequently, is affected by prenatal infections caused by viruses; leads to exacerbated maternal immune activation (MIA), thus contributing to alterations in maternal-fetal neurogenesis, fetal myelinization and is directly involved in the

pathogenesis of disorders of neurodevelopment in the offspring, especially autism[1,5]. This study hypothesizes that maternal infections by COVID-19 during pregnancy are a potential risk for the offspring to develop Autism Spectrum Disorder.

COVID-19 pathophysiology

The pathophysiology of lung involvement by the new coronavirus, SARS-CoV-2, resembles previous viral infections by SARS-CoV and MERS-CoV, presenting an aggressive inflammatory response and repercussion on lung injury. The pathological basis of this new infection seems to be related to injury of the lung cells (type II pneumocytes and capillary endothelial cells), leading to impairment of pulmonary gas exchange (leading to hypoxemia), and perfusion of plasma component exudate into the alveolar space. The integrity of the alveolar epithelium-endothelial barrier is compromised and aggravated by infiltration of pro-inflammatory cells in the interstice and alveolar space[8].

It was escribed two pathophysiological components of SARS-CoV-2; (I) triggered by the virus, cytopathic effect, predominant in the early stage of the disease and (II) the unregulated response of the host organism's immune system, predominant in the late, critical stage of the disease[8].

The overlap of these pathophysiological components is expressed phenotypically in three phases (stages I, II and II) of disease severity; (I) early infection (viral), resulting

from viral replication and activation of the innate immune response, presenting clinical stability and mild symptoms associated with lymphopenia, elevated D-Dimers and Lactate Dehydrogenase (LDH); (II) pulmonary (with or without hypoxia), there is activation of the adaptive immune response, reduction of viremia, initiating an inflammatory cascade with capacity to generate tissue injury, with an acute respiratory distress (dyspnea), and may progress to acute respiratory failure, with an acute lymphopenia, increased Reactive C Protein (PCR) and transaminases and (III) systemic hyperinflammation; multiorganic insufficiency, resulting from a deregulated immune response that triggers the "cytokine storm"[8].

The "cytokine storm" is a reminiscent syndrome of secondary hemophagocytic lymphohistiocytosis (with high expression of the cytokines IL-1, IL-2, IL-7, IL-10 TNF-alpha and to a greater degree IL-6), being an inappropriate hyperinflammatory response to infection, characterized by fever and cytopenias; associated with hyperferritinemia, extreme elevation of PCR, AST/ALT and D-dimer, and reduction of platelets and fibrinogen. This phase is the most severe and mortality phase due to COVID-19[8].

During the unregulated inflammatory phase (stage III), a spectrum of two phenotypes of lung inflammation can also be observed in the respiratory system; (I) type L (*low)*, with hypoxemia associated with vasoplegia by the involvement of the Angiotensin 2 (ACE2) and (II) type H (*high)* receptors with edema and pulmonary filling. The evolution of the L-

spectrum to the H-spectrum results in a synergy of damage induced by self-hyperventilation (with involvement of ACE2 brain receptors) in association with an increase in pulmonary permeability due to the aggravation of the inflammatory process, resulting in a "cytokine storm"[8].

Information on the evolution and possible repercussions of SARS-CoV-2 on pregnancy is still scarce, however, based on information regarding previous coronavirus infections and other viral infections, it is known that there may be complications during the gestational period, with real risk to maternal and child health[1].

Maternal viral infection and ASD

After the rubella pandemic that occurred in 1964, the incidence of autistic born individuals increased from 1% to 13% in the offspring exposed to the virus. Exposure to viral infectious agents during the gestational period 1st or 2nd semester of pregnancy, is correlated to the predisposition to affective and psychiatric disorders in the adult life of the offspring[5].

The exposure to infections during the gestational period, such as flu, measles, herpes, among other infections by pathological agents, may increase the risk of the offspring developing psychiatric disorders, with greater risk of developing autism[5].

The maternal exposure to viral infections, may induce an immune response that may favor the involvement of

diseases, being an important risk factor for the health of the mother as for the health of the offspring[4].

The pregnant women are considered individuals at high risk of morbidity and mortality if exposed to influenza A (H1N1). Seasonal flu increases the risks of hospitalization, especially if contracted in the 2nd or 3rd trimester of pregnancy, increases the probability of birth of premature children and low weight for gestational age[1,9].

Complications during the delivery process affect the neurodevelopment of the fetus and the newborn in later stages of life and may contribute to the involvement of ASD[9]. In studies with large populations, a higher rate of ASD was verified when the maternal infections were severe and required hospitalization of the progenitors[10]. Other studies also highlight the prevalence of ASD in premature born babies[11].

Viral infections during pregnancy result in acute or lasting changes in the development, structure, and function of the fetal central nervous system (CNS). Such alterations increase the risk of premature birth, mental retardation, and neurological disorders in the adult life of the descendants[9,11].

Neurodevelopment is an extremely refined process, occurring predominantly during the prenatal period, with neurogenesis beginning on the 42nd embryonic day, post-conception. During this process, neurons migrate to different brain areas as they are produced, creating rudimentary neural networks from connections with other neurons. Any modification during the activity of brain development, such

as maternal exposure to infectious insults, may compromise the formation of the architecture and function of the fetal brain. Such insults, during the path of normal development of the brain during pregnancy, may trigger a sequence of events that may progressively expand over time, culminating in long-term changes in brain and behavioral functions that may persist until the adult life of the offspring[12].

There is a high risk for the development of ASD in children born during the winter months, because in this period of the year, there is a high prevalence of flu and infectious diseases in pregnant women[13].

There is growing evidence about the etiology of neuropsychiatric diseases being associated to the prenatal environment, since insults to the fetus, during this critical period of neurodevelopment, can modify its brain development, acting as vulnerability factors for mental disorders in adult life, among them ASD[4].

Prenatal viral infection such as rubella and cytomagalovirus can cause damage to the fetus's still immature immune system, leading to increased production of pro-inflammatory cytokines[5]. The real mechanism by which viral infections may trigger ASD is still uncertain, however it is proposed; (1) direct infection in the CNS, (2) infections in other parts of the body, serving as a trigger for CNS diseases, (3) due to alterations in the immune response of the mother or offspring, (4) or a combination of these factors.

It should be noted that during the gestational period, pregnant women are considered immunosuppressed and are more susceptible to infections[1,2]. Cytokines can be directly produced in the brain of the fetus, or even reach the CNS, crossing the immature blood-brain barrier (HBE), thus altering the neurodevelopment[5].

A large study, in 2015, with more than 24,000 cases diagnosed with ASD, showed that there was an increase in ASD rates in the offspring of hospitalized mothers in the year prior to pregnancy; the risk of ASD increased under any hospital diagnosis, including viral and bacterial[14].

More attention should be given to prenatal infectious processes, as there is a strong correlation with the prevalence of ASD in the offspring, in view of the immunological fragility that the maternal organism is subject to, being an easy target for infection during pregnancy[4,5,10]. Also, there is a necessity of immediate and adequate follow-up and treatment to pregnant women in cases of viral infections[15]. However, it is worth noting that the causes of ASD are still unknown, but there is a strong correlation with signs of being multigeneous and multifactorial.

COVID-19 epidemiology in gravities and risk of ASD

During the gestational period, the pregnant women go through several physiological alterations in their organism and may present with immunosuppression, which may increase the risk of developing more serious diseases, becoming more susceptible to respiratory infections[1,2].

Studies related to previous acute respiratory syndrome (SARS-CoV) and Middle Eastern respiratory syndrome (MERS-CoV) coronavirus epidemics in the last two decades have been especially severe, with approximately one-third of infected pregnant women coming to death[1].

Due to physiological alterations in the gestational, immunological, and cardiopulmonary periods, pregnant women are more susceptible to respiratory and systemic complications during processes of viral infections[1,2]. This information is pertinent, as COVID-19 pneumonia progresses rapidly from bilateral consolidation to bilateral diffusion of the pulmonary parenchyma, more readily predisposing to hypoxemic respiratory insufficiency in pregnant women[8].

In influenza A (H1N1) pregnant women made up 1% of those infected but had 5% of deaths. SARS-CoV and MERS-CoV were responsible for a high number of maternal complications, with urgent need for hospitalization; intensive care, need for assisted ventilation, renal failure and death. In pregnant women who had SARS-CoV and MERS-CoV there was a high number of premature births, fetal growth restriction, abortion and fetal death[1,2].

Any serious infection during the gestational period may compromise its evolution, even increasing the risk of premature births[16].

Premature births are an important risk factor for child development problems, including ASD. In a study conducted in Atlanta, Georgia, between 1981 and 1993, it was found that gestational age was associated with twice the increase

in risk for ASD in premature births[17]. There is the possibility that prematurity is correlated with a higher risk of incidence of autism because newborns, who with time developed ASD, presented high rates of this perinatal complication. Prematurity, therefore, is possibly associated with a higher risk of ASD[9,10].

Pregnant women with COVID-19 are more prone to hospitalization and have a higher risk of admission to intensive care units (ICU), with subsequent need for mechanical ventilation than infected non-pregnant women[7].

Autism was also related to fetal suffering, as oxygen deprivation could damage vulnerable regions of the brain, such as the base ganglia, hippocampus, and lateral ventricles. Fetal hypoxia is strongly related to a higher risk of developing autism. The association between ASD and perinatal asphyxia is present in several studies[18]. Researchers have verified that fetal oxygen deprivation increases the risk of TEA and recently, studies have highlighted the occurrence of ASD in very premature babies[9-11].

In short, perinatal factors such as fetal hypoxemia, asphyxia, intrauterine growth restriction, respiratory discomfort syndrome, among others, are associated with the increased prevalence of autism[18].

Of nine pregnancies infected by COVID-19, all had cesarean delivery[19]. Out of 13 pregnant women infected by SARS-CoV-2, five required urgent cesarean section (38%) and six deliveries were premature (46%)[20]. One of the

pregnant women needed intubation for mechanical ventilation. IN other study, it was observed seven cesarean sections and five premature births, the high number of cesarean sections was due to the severity of the clinical picture of COVID-19 infection[21].

The Centers for Disease Control and Prevention (CDC) during the days of January 22nd to June 7th, 2020, verified a total of 8,207 cases of pregnant women infected by COVID-19 in the United States of America (USA). One third (31.5%) of pregnant women were hospitalized compared to 5.8% of infected non-pregnant women. The pregnant women were more likely to be admitted to the ICU and consequently use mechanical ventilation[7].

By May 12, 2020, more than 90 scientific reports of SARS-CoV-2 infection during gravities were published, some cases of critical-stage disease were reported in the third trimester of pregnancy[22]. Most women underwent cesarean section for medical indication (75%), with some cases being necessary due to fetal distress.

In the United Kingdom (UK), about 427 pregnant women were diagnosed with SARS-CoV-2 in 194 hospitals surveyed. One in 10 of these pregnant women admitted with SARS-CoV-2 infection required respiratory support. About 12% of the pregnant women had premature birth due to respiratory compromise[22].

The hospitalizations due to the critical stage involvement by COVID-19 in pregnant women occurred at the end of the second trimester of pregnancy or beginning of

the third trimester, which replicates the pattern observed in other respiratory viral infections that affect pregnant women, such as the Influenza A (H1N1) virus, with high rates of hospitalization in the third gestational trimester[22].

A recent study conducted in Brazil, a survey from the first case of SARS-CoV-2 infection in their pregnant women, February 26, 2020, to June 18, 2020, using the surveillance system for Acute Respiratory Distress Syndrome (ARDS) of the Ministry of Health (MS). The COVID-19 SRDA was diagnosed in 978 pregnant women and in the postpartum period, 207 (21.2%) of these were admitted to the ICU[3].

Maternal immune activation and ASD

The living conditions in the intrauterine environment play an important role in the development of the fetus, changes triggered by various stimuli on the mother can alter the physiological homeostasis of the offspring[23]. The embryonic development, as well as the processes of formation of organs and tissues, can be easily disturbed. Thus, the stimuli received during prenatal life can trigger profound changes in the body and health of the offspring even during adult life[24].

The immune system consists of cells and molecules that defend the body effectively against diseases. Some pathological agents can activate this system, triggering an immune response that protects the body against damage[25]. The Maternal Immune Activation (MIA), interaction between the maternal immune system and infections by different

pathogens, such as viruses, have repercussions on the health of the pregnant woman and the fetus that is still developing. This relationship can have repercussions in alterations in the fetal neurodevelopment, increasing the risk of developing psychiatric disorders in the offspring, since the maternal organism generates an immunological response that, consequently, will produce cytokines, such as IL-6, during the gestational period[5].

Recent studies have hypothesized that the altered expression of pro-inflammatory cytokine levels in the fetal environment in response to MIA may disturb the development of the brain and its neural connections, resulting in possible long-term effects on the individual's mental functions[12].

Pre-clinical evidence and epidemiological data associate the altered levels of expression of pro-inflammatory cytokines in fetal behavior; due to prenatal exposure to immunogenic agents; with the involvement of behavioral alterations in the offspring, and the type of pathological agent, the period of immunoaactivation and the intensity of it, have repercussions on the type of neurological and behavioral change observed in the offspring[26].

In inflammatory processes MIA increases the release of glucocorticoids and the increase in the expression of pro-inflammatory cytokines, such as interleukins 1β (IL-1β), interleukins 6 (IL-6) and tumor necrosis factor α (TNF-α) and/or antibodies in the maternal systemic circulation from MIA, which could easily cross the placental and blood-brain

barrier, acting directly on the fetal brain parenchyma, or initiate a cascade of events in the placenta, blood and brain tissue leading to cytokine production by the fetal astrocytes and microglia. Or the pathological agents can be identified by trophoblast cells and, consequently, initiate the production of cytokines that may act on the fetus. Thus, the cytokines could affect neurodevelopment, acting in migration and differentiation processes resulting in behavioral changes later in the offspring[26-28].

In a recent study, during the process of MIA by viral infection, there is an exacerbated production of pro-inflammatory cytokines, with the concentrations of IL-6 interleukin significantly elevated in the placental environment, which would thus activate the JAK/STAT-3 route, affecting the reduction of placental synthesis of the IGF-1 hormone[29]. Thus, IGF-1 deficiency in the newborn would be correlated with the subsequent development of autism in the newborn, and with the incidence of fever during maternal infection, it would double the risk of autism in the offspring.

This exacerbated production of cytokine IL-6 in the maternal organism was observed in the pathogenesis of previous pandemics; in the Spanish flu of 1918, in the outbreak of SARS-CoV in 2003, in the H5N1 influenza of 1987 and in MERS-Cov in 2012. In a recent report from China, it was found that in the severe stages of COVID-19, besides the "cytokine storm", there was an exaggerated increase of IL-6. It was observed that the lung parenchyma,

in these cases of infection by SARS-CoV-2, expressed in excess the IL-6[29].

Prenatal and perinatal environmental exposures to infectious agents and inflammatory processes are the most well-known risk factors in the literature for ASD involvement in the offspring, as they possibly affect fetal programming. This maternal environment exposed to infections and inflammations has repercussions on a variety of inflammatory cytokines[4,15]. The inflammatory, neurochemical, and neural hypoperfusion abnormalities seem to be the most consistent correlations for the involvement of ASD in the descendants[30].

Thus, viral infections trigger prenatal immunogenic stimuli, consequently leading to MIA, resulting in possible alterations in neurogenesis and fetal myelinization, being causally related to the pathogenesis of neurodevelopmental disorders in the offspring, especially autism[5,8-10].

In recent decades, studies have shown increasing evidence about the etiology of neuropsychiatric diseases, correlating the prenatal environment, where insults to the fetus during this critical moment of development can negatively affect and alter brain development, acting as risk factors for autism in the diagnosis[4,9,10].

Recent findings in covid-19 infected neonates and possible neurodevelopmental disorders

There is evidence that viral infections during the prenatal period, as well as increased expression of pro-

inflammatory cytokines, are "initiators of neurodevelopmental disorders" because they impact maternal immune activation[31]. IL-6, expressed during Maternal Immune Activation (MIA), may influence feto-placental interactions and, consequently, fetal neurodevelopment with increased risk for psychiatric disorders in the offspring. Furthermore, in a longitudinal study, changes in brain architecture, executive function, and working memory skills were verified in neonates at 2 years of age exposed to high levels of IL-6 during pregnancy[31].

In a recent study, it was found that there was transplacental transmission by SARS-CoV-2 in a newborn from an infected mother in the last trimester of gestation and that he presented with neurological impairment. Transmission was confirmed by comprehensive virological and pathological investigations[32]. The infection caused: (1) maternal viremia; (2) placental infection demonstrated by immunohistochemistry and high viral load; (3) placental inflammation, demonstrated by histological examination and immunohistochemistry; and (4) neonatal viremia after placental infection. The nuelo presented with neurological manifestations like those described in adult patients. Neurological symptoms, due to cerebral vasculitis, may also be associated.

The case of a mother with COVID-19 undergoing premature delivery of two fetuses with positive SARS-CoV-2 test was identified in her placental tissues and amniotic fluid. Histological examinations of the placentas showed chronic

intervillositis and extensive intervillous fibrin deposition with ischemic necrosis of the surrounding villi[33].

In a recent literature review, it was seen that of a total of 245 gravidas infected with COVID-19, 89.0% had cesarean deliveries. Of these, 33.3% had gestational complications, there were also 35.3% premature deliveries, and about 2.5% stillbirths or neonatal death. Among the newborns tested, 6.45% had SARS-CoV-234 infection[34].

The studies with placentas, embryos, and brain organoids suggest that fetal organs, including the brain, may also be vulnerable to COVID-19 infection[35]. Furthermore, in a recent case study conducted in Paris, there were transient neurological complications in newborns of pregnant mothers[35].

CONCLUSIONS

Considering the highly sophisticated processes of brain development, any alteration such as maternal exposure to infectious and inflammatory insults that potentially reverberates maternal immune activation can compromise the development of fetal brain architecture and function.

These events can result in alterations in maternal-fetal neurogenesis and neuroanatomical changes, the basis of etiopathogenic theories that are directly involved in the pathogenesis of neurodevelopmental disorders, predisposition to affective and psychiatric disorders.

There are still insufficient data in the literature on the degree of neurodevelopmental impairment of maternal SARS-CoV-2 infection to the embryo. However, the findings so far indicate that there may be potential risks to the fetus, thus greater attention should be paid to these offspring, since prenatal infectious processes may act as an etiological factor to trigger acquired encephalopathies, with the emergence of various types of disorders in the child such as Autistic Spectrum Disorder, as well as mental retardation, schizophrenia, dyslexia, cerebral palsy, epilepsy, and bipolar disorder.

REFERENCES

1.Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol 2020;222:415-26. https://www.ajog.org/article/S00029378(20)30197-6/pdf

2.de Seixas Filho JT, Seyfarth MSC, Cunha DM, da Silveira GRRA, Guedes EF, Orsini M, *et al*. Recomendações de prevenção da saúde materno-infantil na pandemia covid-19 por meio de protocolos médicos. Rev Augustus 2020;25:316-34. https://doi.org/10.15202/1981896.2020v25n51p316

3.Takemoto ML, Menezes MDO, Andreucci CB, Nakamura-Pereira M, Amorim MM, Katz L, *et al*. The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. Int J Gynaecol Obstet 2020;151:154-6. https://doi.org/10.1002/ijgo.13300

4.Atladóttir HÓ, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, *et al*. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 2010;40:1423-30. https://doi.org/10.1007/s10803-010-1006-y

5.Meltzer A, Van de Water J. The Role of the Immune System in Autism Spectrum Disorder. Neuropsychopharmacol 2016;42:284-98. http://dx.doi.org/10.1038/npp.2016.158

6.Misquiatti ARN, Brito MC, Ferreira FTS, Assumpção Júnior FB. Sobrecarga familiar e crianças com transtornos do espectro do autismo: perspectiva dos cuidadores. Rev CEFAC 2015;17:192-200. http://dx.doi.org/10.3389/fncel.2018.00405

7.Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, *et al*. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769-75. https://doi.org/10.15585/mmwr.mm6925a1
8.Marinho A. Janela de Oportunidade para a Imunomodulação na COVID-19 Window of Opportunity for Immunodulatory Therapy in COVID-19. Med Inter 2020;27:3.
https://doi.org/10.24950/rspmi/P.Vista/COVID19/79/20/ CHP/S/2020
9.Hadjkacem I, Ayadi H, Turki M, Yaich S, Khemekhem K, Walha A, *et al*. Fatores pré-natais, perinatais e pós-natais associados ao transtorno do espectrodo autismo. J Pediatr (Rio J) 2016;92:595-601. http://dx.doi.org/10.1016/j.jped.2016.01.012
10.Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand 2012;91:287-300. https://doi.org/10.1111/j.1600-0412.2011.01325.x
11.Gomes PT, Lima LH, Bueno MK, Araújo LA, Souza NM. Autism in Brazil: a systematic review of family challenges and coping strategies. J Pediatr (Rio J) 2015;91:111-21.
https://doi.org/10.1016/j.jpedp.2015.01.005
12.Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, *et al*. Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol 2014;10:643-60. https://doi.org/10.1038/nrneurol.2014.187
13.Zerbo O, Iosif AM, Delwiche L, Walker C, Hertz-picciotto I. Month of conception and risk of autism. Epidemiology 2011;22:469-75. https://doi.org/10.1097/EDE.0b013e31821d0b53
14.Lee BK, Magnusson C, Gardner RM, Blomstrom A, Newschaffer CJ, Burstyn I, *et al*. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun 2015;44:100-5.https://doi.org/10.1016/j.bbi.2014.09.001
15.Bernardi MM, Kirsten TB, Trindade MO. Sobre o Autismo, Neuroinflamação e Modelos Animais para o Estudo de Autismo. Rev Neurocienc 2012;20:117-27.
https://doi.org/10.34024/rnc.2012.v20.8304
16.Mcintosh K. Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention. Uptodate 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention
17.Porto RF, Brunoni D. Transtornos do espectro do autismo: intercorrências perinatais. *In*: D'Antino ME, Brunoni D, Schwartzman JS (Eds.). Contribuições para a inclusão escolar de alunos com necessidades especiais: estudos interdisciplinares em educação e saúde em alunos com transtorno do espectro do autismo no município de Barueri, SP. São Paulo: Memnon Edições Científicas; 2015. p32-41.

18.Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 2011;128:344-55. https://doi.org/10.1542/peds.2010-1036
19.Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13. https://doi.org/10.1542/peds.2010-1036
20.Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect 2020; ahead of print. https://doi.org/10.1016/j.jinf.2020.02.028
21.Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, *et al*. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9:51-60. https://doi.org/10.21037/tp.2020.02.06
22.Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, *et al*. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107. https://doi.org/10.1136/bmj.m2107
23.Nunes MC, Madhi SA. Review on the effects of influenza vaccination during pregnancy on preterm births. Hum vaccin immunother 2015;11:2538-48. https://doi.org/10.1080/21645515.2015.1059976
24.Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the dutch famine and disease in later life: an overview. Reprod toxicol 2005;20:345-52. https://doi.org/10.1016/j.reprotox.2005.04.005
25.Murphy K, Weaver C. Janeway's immunobiology. 9ª edição. New York (EUA): Garland Science, 2016. https://books.google.com.br/books?hl=pt-BR&lr=&id=GmPLCwAAQBAJ&oi=fnd&pg=PP1&dq=MURPHY,+2016&ots=6ayh0by-vh&sig=bfgOQkT2xmU8KHIwYEFzuaHEhKQ#v=onepage&q=MURPHY%2C%202016&f=false
26.Meyer U. Prenatal poly(i:c) exposure and other developmental immune activation models in rodent systems. Biol psychiatry 2014;75:307-15. https://doi.org/10.1016/j.biopsych.2013.07.011
27.Depino AM. Peripheral and central inflammation in autism spectrum disorders. Cell Mol Neurobiol 2012;53:69-76. https://doi.org/10.1016/j.mcn.2012.10.003
28.Soares EDCC. A ativação imunológica materna na gênese do comportamento autista: aspectos comportamentais e neuroquímicos. [monografia]. Tubarão: Universidade do Sul de Santa Catarina – UNISUL; 2014. http://www.riuni.unisul.br/handle/12345/2039
29.Steinman G. COVID-19 and autism. Med hypoth 2020;142:109797. https://doi.org/10.1016/j.mehy.2020.109797
30.Yang WH, Jing J, Xiu LJ, Cheng MH, Wang X, Bao P. Regional cerebral blood flow in children with autism spectrum disorders: a quantitative mTc-ECD brain SPECT study with statistical parametric mapping evaluation. Chin Med J (Engl) 2011;124:1362-6. https://doi.org/10.3760/cma.j.issn.0366-6999.2011.09.017

31.Martins-Filho PR, Tanajura DM, Santos HP, Santos VS. COVID-19 during pregnancy: Potential risk for neurodevelopmental disorders in neonates? Eur J Obstet Gynecol Reprod Biol 2020;250:255-6. https://doi.org/10.1016/j.ejogrb.2020.05.015
32.Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Cao J, *et al*. Transplacental transmission of SARS-CoV-2 infection. Nature Comm 2020;11:3572. https://doi.org/10.1038/s41467-020-17436-6
33.Pulinx B, Kieffer D, Michiels I, Petermans S, Strybol D, Delvaux S, *et al*. Vertical transmission of SARS-CoV-2 infection and preterm birth. Eur J Clin Microbiol Infect Dis 2020;39:2441-5. https://doi.org/10.1007/s10096-020-03964-y
34.Chamseddine RS, Wahbeh F, Chervenak F, Salomon LJ, Ahmed B, Rafii A. Pregnancy and neonatal outcomes in SARS-CoV-2 Infection: a systematic review. J Pregnancy 2020:4592450. https://doi.org/10.1101/2020.05.11.20098368
35.Varma P, Lybrand ZR, Antopia MC, Hsieh J. Novel targets of SARS-CoV-2 spike protein in human fetal brain development suggest early pregnancy vulnerability. Front Neurosc 2021;14:614680. https://doi.org/10.3389/fnins.2020.614680