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EDITORIAL
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# Could Maternal COVID-19 Disease be a Risk Factor for Neurodevelopmental Disorders in the Child?

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Although the etiology of neurodevelopmental disorders has not been elucidated, recent theories suggest that genetic and environmental factors play a role. Neurodevelopmental disorders were defined as mutations of genes coding synaptic adhesion molecules, scaffolding proteins, synaptic communication proteins, protein synthesis, and degradation associated with synapse functions; however, genetic factors can explain the etiology only in a limited number of cases.[1] The relationship between synaptogenesis genes and neurodevelopmental disorders has led to questioning the role of environmental factors in synapse function. Understanding the role of microglia-derived cytokines in synaptic pruning and central nervous system cytokine levels being affected by environmental factors such as maternal viral and bacterial infections, toxins, perinatal hypoxia, maternal stress, and maternal obesity supported this idea. Microglia and immune molecules (cytokines, chemokines, etc.) are critical for normal development, but their overexpression can result in abnormal development.[2] As a result, immune activation and immunologic abnormalities in the brain may affect the developing brain by playing a pivotal role in the etiology and/or progression of neuropsychiatric disorders such as autism spectrum disorders (ASD), depression, schizophrenia, and Alzheimer's disease.

Maternal viral, bacterial, or even parasitic infections were shown to cause maternal immune activation. Maternal immune activation can cause fetal brain damage by causing immune system changes with microglia activation and increased proinflammatory cytokines. For women whose children were later found to have neurodevelopmental disorders, proinflammatory cytokine levels are high in samples taken during pregnancy. Some of the cytokines can cross the placenta and the fetal blood–brain barrier. These cytokines can potentially cause fetal microglia and mast cell activation and can create a favorable environment for the formation of neurodevelopmental disorders.[3,4] Neurodevelopmental effects of cytokine signals were shown in cell cultures and animal models. Although the relationship between congenital viral infections and neurodevelopmental disorders has not been defined for every virus, it is known for many years that maternal influenza virus infection increased the frequency of ASD and schizophrenia, and congenital cytomegalovirus infection causes cognitive abnormalities and sensorineural deafness in the offspring.[5] In recent years, a similar relationship was reported for congenital Zika virus infection.[6] Pregnant women are also affected by pandemic SARS-CoV-2 infection, but neurodevelopmental effects of maternal SARS-CoV-2 virus infection are not yet known.

Few studies are investigating the prevalence of COVID-19 disease in pregnant women. COVID-19 disease was reported in women presenting for labor at a center in the United States as 15.4% (13.5% asymptomatic, 1.9% symptomatic).[7] In another study conducted in the same country, SARS-CoV-2 virus positivity was found as 12.2% for all trimesters of pregnancy.[8] It is understood from these studies that the frequency of COVID-19 disease in pregnancy is high. It has been reported that the balance of regulatory T cell/TH17 increased in favor of TH17 in COVID-19 disease.[9] Immunity shifted to the TH17 direction increases the release of proinflammatory cytokines. Decreased regulatory T cells and increased TH17 cells are associated with obstetrics complications such as abortions, prematurity, and preeclampsia. Although some studies have reported that COVID-19 disease in pregnant women is not

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different in non-pregnant women, in some studies, it is stated that COVID-19 disease-related morbidity increases in pregnancy. It has been reported that the morbidity rates in women undergoing COVID-19 disease in pregnancy do not differ from the normal population and women without COVID-19 disease. However, it was observed that pregnant women with COVID-19 disease had more intensive care unit hospitalization and mechanical ventilator requirements.[10] There are also studies reporting that mortality is higher in women who have had COVID-19 disease during pregnancy.[11] Although the effect of COVID-19 disease on pregnancy prognosis is controversial, SARS-CoV-2 infection especially after 20th gestational week was found to be associated with prematurity and low birth weight.[12] However, the effects of COVID-19 disease on fetal brain are not known.

There are not enough observational studies in terms of behavioral and neurologic problems that maternal coronavirus infections can cause brain damage in children.[13] In a meta-analysis consisting of 7865 COVID-19 disease cases, lower lymphocyte count including CD4+, CD8+, CD3+ T cells, CD19+ B cells, natural killer cells, and monocytes, and higher leukocyte and neutrophile, C-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin, serum amyloid A, interleukin (IL)-2, IL-2R, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha, and interferon gamma have been reported in severe cases compared to mild–moderate cases. However, there was no difference in IL-1β, IL-17, and CD4+/CD8+ T cells ratio between severe and mild cases.[14] Since these changes are similar to those described in influenza H1N1 infection, it is seen that different viral infections act through a common mechanism. Because the maternal immune response to the SARS-CoV-2 virus is similar to other viruses that cause influenza-like illness in pregnancy, it is thought that neurologic and/or behavioral problems may occur in the children of women who have had COVID-19 disease in pregnancy.

Vertical transmission of the SARS-CoV-2 virus in pregnancy is rare. According to nasopharyngeal swab SARS-CoV-2 viral RNA and IgM SARS-CoV-2 antibody positivities in newborns, the vertical transmission was found to be 3.2% and 3.7%, respectively.[15] In children of women with a history of viral infection in pregnancy, neurologic and behavioral problems were possibly explained by direct exposure of the virus to the fetal brain or activation of astrocytes and microglia by the stimulation of fetal inflammatory response. Activation of astrocyte and microglia negatively affects the fetal brain by cytokine release, apoptosis, slowing of growth, and direct cell effects.[16] Since vertical transmission of the SARS-CoV-2 virus is limited during pregnancy, possible neurodevelopmental influence may be related to fetal inflammation induced by maternal immune activation and resultant fetal brain damage. Animal and epidemiologic studies have been shown that neurologic and behavioral disorders can develop in children without placental transmission of the virus in women who had a viral infection during pregnancy.[16,17] Different viral infections, such as acute respiratory syndrome due to influenza H1N1 virus, have been shown to adversely affect a child's health, even infection is limited to maternal or placenta, and without fetal infection.[18,19] The relation between placenta-confined viral infection and fetal brain injury has also been described. Inflammatory mediators or cells in the placenta can be transferred to the fetus and may damage the fetal brain through the release of cytokines, neurotransmitters, or excitotoxic substances.[13] Neurological and mental problems developing in a child due to maternal Zika virus infection is one of the best examples of the harmful effects of viruses on the fetal brain. It has been reported that neurodevelopmental abnormalities may occur in fetuses exposed to Zika virus in utero, even congenital Zika virus infection does not develop.[20]

Recent studies show that there may be a relationship between maternal viral infections and ASD. In a study evaluating 1,612,342 children born between 1980 and 2005 in Denmark, it has been shown that the risk of ASD increases approximately 3 times in the children of women who have had viral infections in the first trimester of pregnancy.[13] An increase of ASD was also noted in the children of women who had a bacterial infection in the second trimester of pregnancy (adjusted relative risk 1.42). In a meta-analysis, more than 40,000 ASD cases were evaluated from 15 studies, and infectious exposure in the prenatal period was found 1.13 times more.[21] In animal studies, maternal immune activation (MIA) has been shown to cause behavioral changes in the child with an intense inflammatory response. Rodent's MIA model showed that maternal IL-17a disrupts cortical development and causes behavioral abnormalities in the child. These effects can be mitigated when an anti-IL-17a blocker is used.[22] In the same animal model, it was shown that increased IL-6 levels were associated with behavioral abnormalities in the child, and social problems could be reduced with anti-IL-6 antibodies.[23] Although the relationship between maternal COVID-19 disease and ASD or psychotic abnormalities in the offspring is not yet well understood, regular and close follow-up is recommended for neurologic and psychiatric development of children of women who had COVID-19 disease in pregnancy.

As a result, the COVID-19 disease also affects pregnant women. In women who have had COVID-19 disease in the pregnancy, data on morbidity and mortality as well as increased rates of abortion, prematurity, and low-birth-weight of the offspring were reported. However, there is not enough data to show long-term risks for ASD and cognitive disabilities in children of women with COVID-19 disease in pregnancy. To answer this question, long-term studies with systematic follow-up and detailed neurologic assessment of children with a maternal history of COVID-19 disease are required.

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