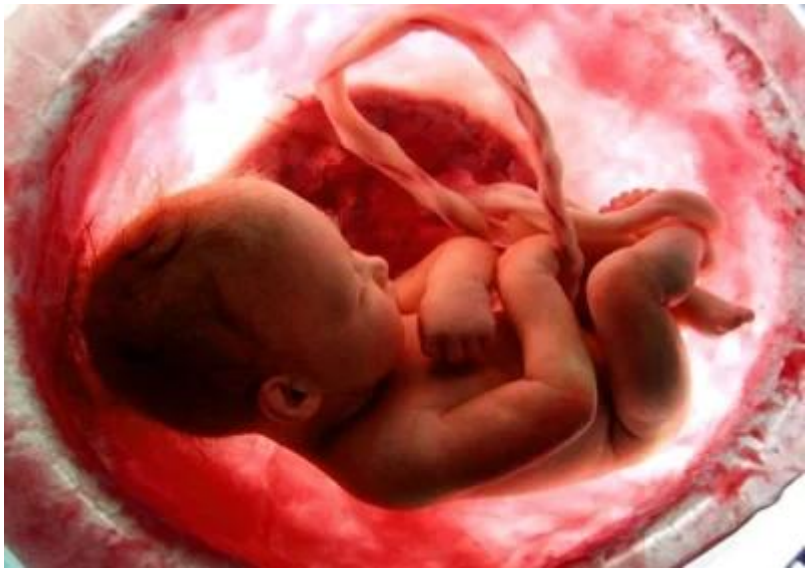
Some recent evidence suggests that maternal infection with severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) during pregnancy may be associated with a greater rate of numerous complications in infected mothers and their newborns. The complications observed in mothers include preeclampsia, preterm birth, and miscarriages, whereas complications observed in newborns exposed to maternal COVID-19 *in utero* include neurodevelopmental delay, motor deficits, seizures, and microcephaly. In this study, American scientists reported severe neurodevelopmental sequelae in two neonates and placental pathology after *in utero* SARS-CoV-2 exposure.

The negative influence of *in utero* infections on fetal development and long-term outcomes was well documented for numerous viral pathogens, including Zika virus, herpes simplex virus, human immunodeficiency virus (HIV), and others. They possess the capability to cross the placenta and infect fetal tissues leading to placental pathology, fetal injuries, and long-term sequelae in the offspring, including neurodevelopmental disorders. The central nervous system (CNS) manifestations of AIDS in children differ markedly from those in adults. The most common CNS presentation of AIDS in children is encephalitis, characterized by generalized parenchymal atrophy, white matter lesions that spare the U-fibers, and symmetric vascular calcifications in the basal ganglia. In HIV-related cerebral vasculopathy, the inflammation begins in the adventitia and involves the *vasa vasorum*. This leads to ischemia of the arterial wall, destruction of the elastic lamina, subintimal fibrosis, panarteritis, stenosis, and aneurysmal arterial dilatation. (Shah SS et al. Cerebrovascular complications of HIV in children. Am J Neuroradiol 1996, 17 (10) 1913-1917.) http://www.ajnr.org/content/17/10/1913



SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases.

Case 1: A premature infant

A male infant of 32 weeks gestational age, appropriately grown, was born with Apgar scores of 4 and 7. The mother was healthy until 27 weeks of gestation when she was admitted to the intensive care unit for pneumonia and multisystem disease, diagnosed as COVID-19 by positive reverse transcription polymerase chain reaction (rt-PCR) for SARS-CoV-2.

After the birth, the newborn immediately had a seizure-like activity and poor respiratory efforts, which required intubation and assisted ventilation. The initial chest radiograph showed bilateral confluent densities, that were not completely resolved after full respiratory recovery. The conventional electroencephalography (EEG) revealed a frequent occurrence of multifocal epileptiform discharges, consistent with a diagnosis of *status epilepticus*. At 24 hours of age, the newborn's RT-PCR test for SARS-CoV-2 was negative, but laboratory tests showed IgG, combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of SARS-CoV-2 spike protein, and markedly elevated serum levels of inflammatory markers and cytokines.

After three months, the infant was discharged with microcephaly and seizures. At 12 months of age, neurologic examination was abnormal, with head lag, truncal hypotonia,

hyperreflexia, and delayed developmental milestones.

At 13 months of age, the infant suddenly died. The results of the brain autopsy revealed a significant reduction in brain weight and cerebral white matter volume, enlarged ventricles, and extensive gliosis.

The SARS-CoV-2 S1 protein, colocalized with the N protein, was detected by immunofluorescence throughout the infant's brain.

Case 2: Full-term infant

A female infant, 39 weeks of gestational age, appropriately grown, was born with Apgar scores of 4 and 6. The mother reported an asymptomatic SARS-CoV-2 positivity in the late second trimester, followed by a negative test. Although asymptomatic, she tested positive again at the time of vaginal delivery, which was complicated by chorioamnionitis. The infant had apnea and required nasal continuous positive airway pressure. Antibiotics were administered for suspected sepsis. Neurological examination was normal except for mild hypotonia. At 16 hours of age, she developed seizures confirmed by EEG.

At 24 hours of age, her RT-PCR test for SARS-CoV-2 was negative, but immunofluorescence analysis showed IgG, combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of SARS-CoV-2 S protein, and elevated serum levels of inflammatory markers and cytokines. There was a cerebrospinal fluid pleocytosis, but no viruses or bacteria were detected.

At three months of age, the results of brain magnetic resonance imaging revealed severe parenchymal atrophy and cystic encephalomalacia. At one year of age, the child had microcephaly and significant neurodevelopmental delay, with low axial tone, head lag, hyperreflexia, clonus, and the inability to roll over or sit unsupported.

Placental findings

Both placentas were analyzed for inflammatory and modulating factors that directly or indirectly adversely affect fetal central nervous system development. These findings were compared with those of placentas from two age- and gender-matched SARS-CoV-2 negative mothers. The concentrations of inflammatory and oxidative stress markers, such as macrophage inflammatory protein 1β (MIP1-β), stromal cell-derived factor 1, interleukin 13, and interleukin 10 were increased in the placentas of mothers who were infected with

SARS-CoV-2 during pregnancy compared to controls.

In both placentas, the histopathological examination demonstrated thrombosis and recanalization of stem villous vessels, stromal fibrosis, and increased stromal karyorrhexis of the terminal villi. Thrombosis and apoptosis in placental tissue were associated with maternal-fetal vascular malperfusion, placental ischemia, and deterioration of placental function.

The authors noted that inflammation of the fetal-placental unit leads to a syndrome of fetal inflammatory response, fetal hypoxia, compromise of the fetal blood-brain barrier, and brain injury. The elevated concentrations of placental pro-inflammatory MIP1-β and IL-13 were previously shown to impair fetal neurodevelopment.

Additionally, placental human chorionic gonadotropin (hCG) was markedly decreased in the SARS-CoV-2-positive placentas. This hormone induces uterine angiogenesis and vasculogenesis to ensure adequate blood supply to the placenta and protects the developing fetal brain from hypoxic neurodegeneration. Accordingly, the authors stated that a decreased concentration of placental hCG suggests a placental compromise.

The SARS-CoV-2 N and S proteins were identified by immunofluorescence in the syncytiotrophoblast of both placentas.

Conclusion

The study reported cases of two infants born in the third trimester to mothers who were infected with SARS-CoV-2 during pregnancy. Both mothers tested positive for SARS-CoV-2 several weeks before delivery. At birth, neither infant was positive for SARS-CoV-2. However, both infants had IgG, combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of SARS-CoV-2 S protein, and markedly elevated serum levels of inflammatory markers and cytokines.

Clinical findings, placental pathology, and immunohistochemical analysis strongly suggest that second-trimester maternal SARS-CoV-2 infection and placentitis triggered an inflammatory response in the fetoplacental unit that affected the fetal brain. A recent animal study has also shown maternal-fetal transmission of SARS-CoV-2 that occurred in later stages of mice pregnancy, at time points matching the second and third trimesters of human pregnancy. The infection level was much higher at the time corresponding to the third trimester in humans. Virus demonstrated tropism for various fetal brain cells, including

endothelial cells of blood vessels, barrier cells of the choroid plexus, neurons, and glial cells.
https://discovermednews.com/experimental-evidence-of-maternal-fetal-transmission-of-sars-cov-2-and-viral-tropism-for-fetal-brain-cells/

Although the virus was not detectable in the nasopharyngeal swabs of two newborns, the presence of anti-SARS-CoV-2 antibodies and the elevated levels of proinflammatory mediators, together with the neuropathological findings in the brain of the deceased infant, indicate that brain damage was caused either by the placental infection or/and by an undetected infection of the fetal brains *in utero*.

The immunofluorescence findings of SARS-CoV-2 S1 and N proteins in both the placentas and the brain of the deceased infant raise the possibility that undetected *in utero* infection of the fetal brains with SARS-CoV-2 has directly contributed to brain damage.

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Journal Reference

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