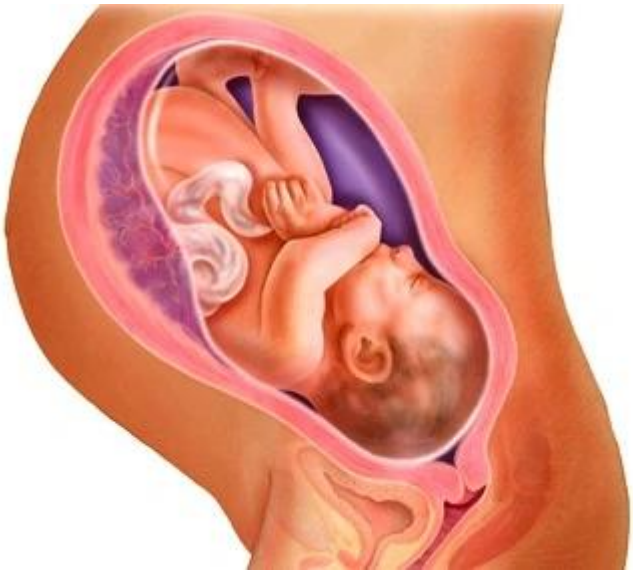
Previous studies have shown that maternal infection with severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) during pregnancy may be associated with a greater rate of numerous complications in infected mothers and their newborns. However, maternal morbidity and mortality, neonatal complications, and the underlying pathophysiological mechanisms remain under-researched. In this study, the authors from the United States investigated whether stool samples from preterm and term newborns who tested negative for SARS-CoV-2 at birth and born to mothers who had COVID-19 during pregnancy could contain SARS-CoV-2 RNA and S protein from the first day of life to two months of age.

The complications observed in mothers infected with SARS-CoV-2 during pregnancy 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. A recent study reported severe neurodevelopmental sequelae in 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. The SARS-CoV-2 N and S proteins were detected in the brain of the deceased infant and both placentas. The placentas from both mothers showed thrombosis, loss of stromal vessels, and apoptosis. Clinical findings, placental pathology, and immunohistochemical analysis strongly suggested that second-trimester maternal SARS-CoV-2 infection and placentitis triggered an inflammatory response and oxidative stress injury to the fetoplacental unit that affected the fetal brains.
https://discovermednews.com/neurodevelopmental-sequelae-microcephaly-in-newborns-after-in-utero-exposure-to-sars-cov-2/

This pathology of placental arteries is consistent with another study of placental arteries in women who had COVID-19 during pregnancy and gave birth to live full-term newborns. These results showed severe vascular remodeling of the placental arteries, including severe thickening of the vessel walls and occlusion of the vessel lumen. The placental artery wall thickness was twice as high in women with COVID-19 during pregnancy than in women without COVID-19. The arterial lumen was 5-fold smaller in women with COVID-19 than in the control subjects.
https://discovermednews.com/severe-vascular-remodeling-of-placental-arteries-in-women-with-sars-cov-2-during-pregnancy/



***About the Study and Results***

The study included 14 preterm and term newborns, born at 25–41 weeks of gestational age, whose mothers had COVID-19 during pregnancy. All newborns had negative reverse transcription polymerase chain reaction (rt-PCR) of nasopharyngeal swabs for SARS-CoV-2 at birth. Eleven of fourteen mothers tested positive for SARS-CoV-2 more than ten weeks before delivery, and they did not have any active symptoms of COVID-19 during delivery, making direct contact, droplet, or airborne transmission unlikely. A control group consisted of 30 newborns, born to mothers who had not been diagnosed with COVID-19 during pregnancy. When possible, stool samples were taken from each newborn from the first day of life, and every week thereafter up to 87 days of life. The newborn's stool was tested for SARS-CoV-2 RNA and S protein, and the inflammatory cytokines interleukin (IL)-6) and interferon (IFN)-γ.

SARS-CoV-2 RNA and S protein were detected in the stool specimens collected from eleven of fourteen newborns as early as the first day of life. The S protein was consistently detected at high levels in stool samples of approximately 30% of infants. Increased levels of proinflammatory IL-6 and IFN-γ were found in stool homogenates from all 14 newborns.

The majority of newborns were clinically well, except for two. One preterm neonate immediately after birth developed severe liver failure. He tested negative for SARS-CoV-2 several times but had positive serum IgG antibodies for SARS-CoV-2. The infant died at 11 weeks of age due to complications of liver insufficiency. The autopsy results were consistent

with the diagnosis of gestational alloimmune liver disease (GALD). Increasing levels of viral RNA were detected in his stool samples until day 56. Another preterm newborn died from necrotizing enterocolitis (NEC). Increasing levels of the S protein were detected in her stool specimens from the first day of life to day 87.

According to the authors, it remains unknown whether the intestinal reservoir of SARS-CoV-2 could have contributed to the development of GALD or NEC in two deceased newborns. However, the increase in viral RNA and S protein levels over time in these two infants suggests viral replication.

*Conclusion*

This study showed that stool samples from newborns, born to mothers with COVID-19 infection during pregnancy and tested negative for SARS-CoV-2, contained SARS-CoV-2 RNA and S protein at delivery.

Since the fecal samples were collected as early as the first day of life, these findings suggest *in utero* transmission of the SARS-CoV-2 to the intestine of the fetus, and possible persistent intestinal viral reservoirs in newborns. The authors suggested that *in utero* viral transmission likely occurs during early gestation, before 27 weeks. The mechanism of *in utero* transmission to the fetal intestine remains unclear. Since viral RNA was detected in the placenta and amniotic fluid, this might be the pathway of viral transmission.

As the gut microbiome strongly influences the early development of the immune system, the findings of SARS-CoV-2 RNA and S protein, as well as the increased levels of proinflammatory cytokines in the newborn intestines, could influence the development of the gut microbiome and the immune landscape, potentially impacting the susceptibility to diseases later in life.

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