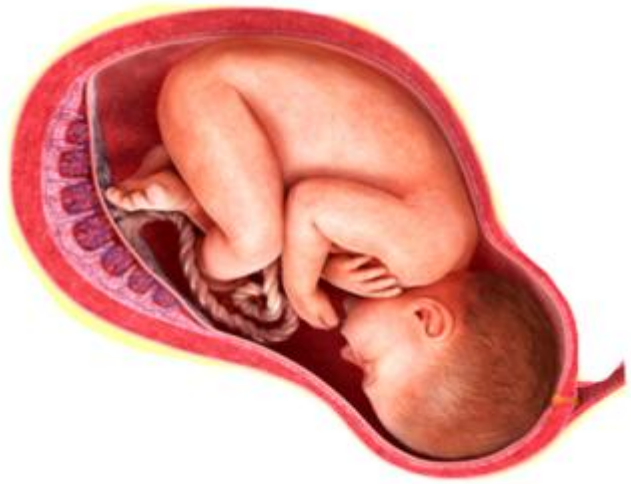
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. In this study, the authors from the United States investigated whether stool samples from preterm and term newborns, with negative reverse transcription polymerase chain reaction (rt-PCR) of nasopharyngeal swabs for SARS-CoV-2 and born to mothers who had coronavirus disease 2019 (COVID-19) infection during pregnancy, could contain viral RNA and S protein from the first day of life to two months of age. The results showed that SARS-CoV-2 RNA and S protein were detected in the feces of the newborns at delivery, indicating viral transmission *in utero* to the fetal intestine.

Previous studies have shown that mothers who tested positive for SARS-CoV-2 during pregnancy may have adverse pregnancy outcomes. However, maternal morbidity and mortality, neonatal complications, and the underlying pathophysiological mechanisms remain under-researched. One previous morphometric study of the placental arteries in women who suffered from COVID-19 during pregnancy and gave birth to live full-term newborns demonstrated severe vascular remodeling of the placental arteries, including severe thickening of the vessel walls and occlusion of the vessel lumen. The thickness of the arterial walls of the placenta in women with COVID-19 was twice as high as in women without COVID-19. The arterial lumen was significantly smaller (5-fold) 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/

Another study reported severe neurodevelopmental sequelae in two neonates after *in utero* exposure to SARS-CoV-2, with N and S proteins detected in the brain of the deceased infant and both placentas. The placenta from both mothers showed thrombosis, loss of stromal vessels, and apoptosis. According to the authors, mid-trimester maternal SARS-CoV-2 infection with placentitis triggered an inflammatory response and oxidative stress injury to the fetoplacental unit. This in turn affected the fetal brain.
https://discovermednews.com/neurodevelopmental-sequelae-microcephaly-in-newborns-after-in-utero-exposure-to-sars-cov-2/



About the study

The study included preterm and term newborns whose mothers had COVID-19 during pregnancy. All newborns tested negative for SARS-CoV-2 at birth (rt-PCR of nasopharyngeal swab).

Eleven of fourteen mothers had COVID-19 and tested positive for SARS-CoV-2 more than ten weeks before delivery. They did not have any active symptoms of COVID-19 during delivery, making direct contact, droplet, or airborne transmission unlikely.

All stool samples were taken from the first day of life if possible, from each newborn, and every week thereafter for a maximum of 87 days of life. Newborn stools were examined for SARS-CoV-2 RNA and S protein, and the inflammatory cytokines interleukin-6 (IL-6) and interferon-gamma (IFN-γ).

Results

The study included 14 preterm and term newborns, born at 25–41 weeks of gestational age, and a control group of 30 neonates of mothers who had no reported or documented COVID-19 in pregnancy. 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 serum IgG antibodies were positive for SARS-CoV-2. The infant died at 11 weeks of age due to complications of liver insufficiency. The autopsy results were consistent with his clinical diagnosis of gestational alloimmune liver disease (GALD). Importantly, 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.

The stool specimens collected from eleven of fourteen newborns contained viral RNA and S protein as early as the first day of life. Enzyme-linked immunoassay test consistently detected high levels of the S protein in five neonates, and an increase of the S protein levels over time in four neonates. In addition, in stool homogenates from all 14 newborns, increased levels of proinflammatory IL-6 and IFN-γ were found.

Conclusion

This study has shown that stool samples from newborns, born to mothers with COVID-19 infection during pregnancy and tested negative for SARS-CoV-2, contained viral RNA and S protein at delivery. The S protein was consistently detected at high levels in stool samples of approximately 30% of infants. 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.

The gut microbiome strongly influences the early development of the immune system. The authors emphasized that viral RNA and S protein and elevated levels of proinflammatory cytokines in the newborn intestines may affect the gut microbiome development and immune landscape, potentially influencing the susceptibility to diseases later in life.

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