Numerous viral pathogens, including Zika virus, HSV, HIV, and others possess the capability to cross the placenta and infect fetal tissues, resulting in mild to severe neurological complications. Some previous data have shown the potential for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to infect the placenta and fetal tissue. In this article, the authors from the United Kingdom studied the susceptibility of the human fetal brain to SARS-CoV-2 during early pregnancy. They investigated the presence of SARS-COV-2 antigens in the human fetal brain, specifically in fetal cortical hemorrhages, and in the placenta, amnion, and umbilical cord during early gestation (first and second trimester of pregnancy).

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. Two host-cell factors are important for SARS-CoV-2 viral entry into a number of cell types: angiotensin-converting enzyme 2 (ACE2), which is bound by S-protein, and transmembrane protease, serine 2 (TMPRSS2), which cleaves S-protein, allowing this binding to take place.

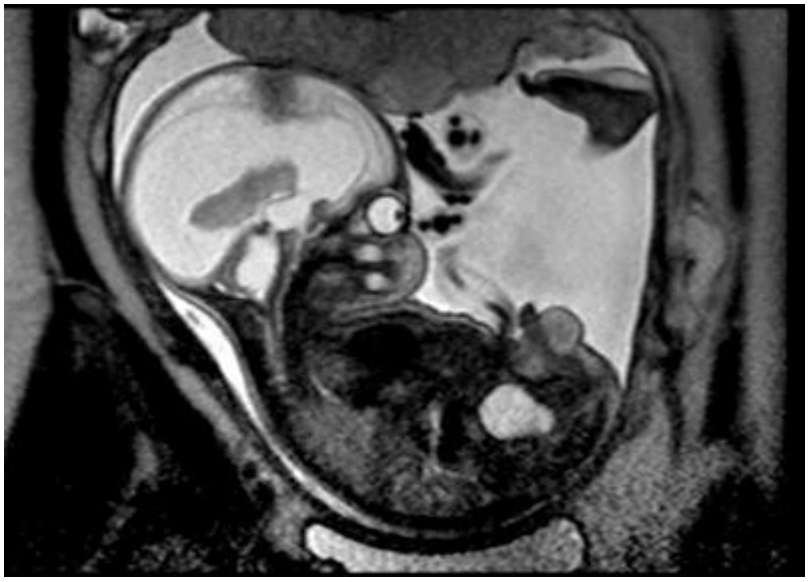
Of note, a recent study described neurodevelopmental sequelae in two neonates after *in utero* exposure to SARS-CoV-2. Both mothers tested positive for SARS-CoV-2 several weeks before delivery. At birth, neither infant was positive for SARS-CoV-2. However, both infants had IgG, combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of the SARS-CoV-2 S protein. 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.
https://discovermednews.com/neurodevelopmental-sequelae-microcephaly-in-newborns-after-in-utero-exposure-to-sars-cov-2/

About the study

The 661 tissue samples of human fetuses between 9 and 21 weeks gestational age were collected in the Human Development Biology Resource (HDBR) for 21 months. The majority of fetal samples, 599, were from elective abortions with no detected abnormalities, whereas 62 samples were of fetuses with a chromosomal trisomy (44 trisomy 21, 12 trisomy 18, 1 trisomy 16, 1 trisomy 13, and 3 triploid).

Results

Brain cortical hemorrhage was found in 26 of 661 fetal tissue samples. Of 26 hemorrhagic samples, 25 were from elective terminations (no abnormalities were recorded), and one sample was from a fetus with trisomy 21. The authors emphasized that this finding of 26 cortical hemorrhages in 661 fetal tissue samples is highly unusual. In comparison, only two cases of cortical hemorrhages were found in 300 brain samples randomly selected from 4917 Human Development Biology Resource fetuses. Importantly, the fetal brain samples with cortical hemorrhage were received in the Human Development Biology Resource when the number of confirmed COVID-19 cases was the highest in the UK.

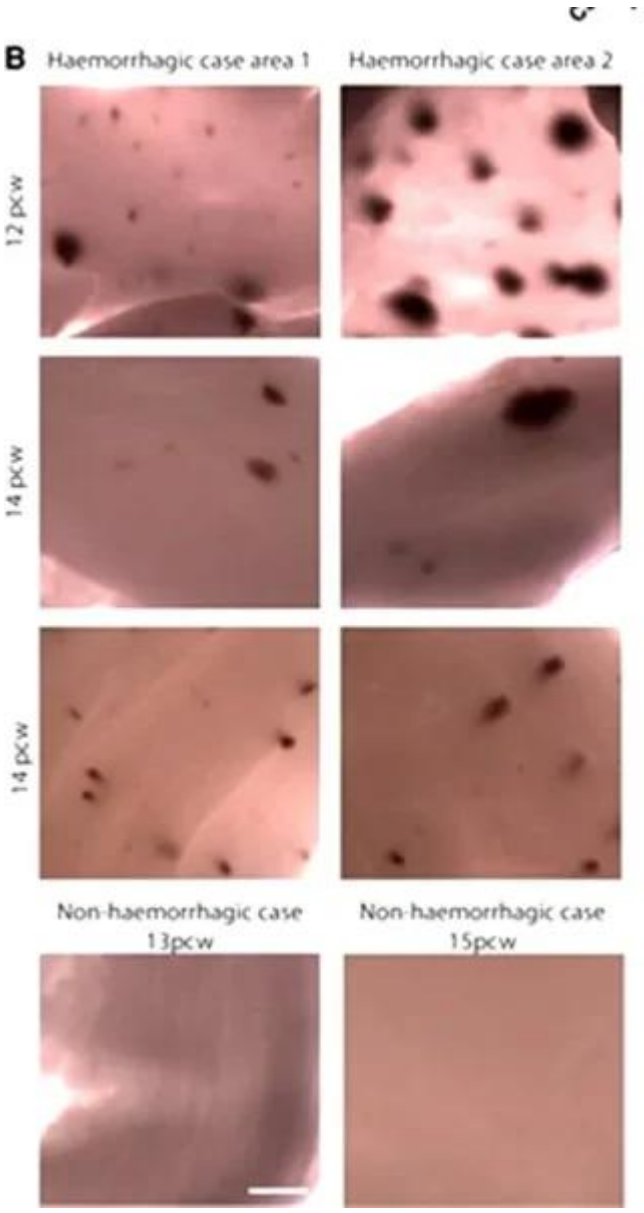


Fetal brain hemorrhage

The cortical hemorrhages were found in fetuses between 8 and 22 weeks of gestational age, and most of the hemorrhages (57.6%) were in fetuses between 12 and 14 weeks of gestational age. Cortical iron deposition, which occurs after the red blood cell lysis, confirmed that recent hemorrhages were more frequent in the samples of younger fetuses (between 12 and 14 weeks of gestational age) than in the older ones (between 19 and 21

weeks of gestational age).

The numbers of the brain macrophages (CD68 positive cells), IBA-1 positive brain macrophages, and monocytes positive for the marker s100a9 were significantly increased in the hemorrhagic cortex compared to non-hemorrhagic and pre-pandemic cortical samples. Lymphocyte infiltration was not present.



The pictures from the original article of Massimo M et al, Brain 2023.

The presence of SARS-CoV-2 proteins in the fetal and maternal tissue samples

Five of the 26 hemorrhagic cortical tissue samples contained the choroid plexus tissue, which has been previously reported as particularly vulnerable to SARS-CoV-2 infection due to a high expression of ACE2. In all five choroid plexuses from the hemorrhagic cortical samples, immunofluorescence detected significantly higher concentrations of the S and N proteins (on average 2.5 times above background staining) than in non-hemorrhagic cortical samples. A low level of the S protein was detected in one choroid plexus of the non-hemorrhagic cortical sample.

A low level of the S protein (on average 1.3 times above background) was found in the cortical tissue, and there was no significant difference between non-hemorrhagic/or hemorrhagic samples and pre-pandemic controls. Cortical tissue samples of fetuses between 12 and 14 weeks of gestational age had the highest levels of the S protein.

One fetal sample at 9 weeks of gestational age contained the S protein in the cerebral cortex, amnion, and umbilical cord. Another fetal sample at 11 weeks of gestational age contained the S protein in the cerebral cortex and placenta, and a third fetal sample at 13 weeks of gestational age contained the S protein in the cerebral cortex and umbilical cord. These findings confirm that S protein was present in tissues of fetal and maternal origin.

The assessment of the blood vessels' integrity in cortical tissues by quantifying the endothelial tight junction protein claudin-5 demonstrated that hemorrhagic samples had a higher percentage of blood vessels negative for claudin-5 than non-hemorrhagic samples. These findings indicate reduced endothelial cell integrity within the blood vessels in hemorrhagic cortical samples.

Conclusion

This study reported the presence of SARS-CoV-2 in fetal brain tissue, associated with cortical hemorrhages, and linked to reduced blood vessel integrity and monocyte infiltration

of the hemorrhagic cortex. The SARS-CoV-2 S and N proteins were abundantly found in the choroid plexus of the hemorrhagic cortex and were positive in all brain hemorrhagic samples. Low levels of the S protein were detected in the cortical neurons and progenitor cells, in the placenta, amnion, and umbilical cord, and in one of the non-hemorrhagic samples of the choroid plexus.

Importantly, the majority of hemorrhages were detected in samples from the late first and early second trimester of pregnancy, which is a critical window of human fetal brain development.

According to the authors, these results suggest that the human brain is highly susceptible to SARS-CoV-2 during early gestation. Further research is needed to determine whether effects on cortical tissue found in this study are long-lasting, or can regress with minimal consequences.

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Journal Reference

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