Transplacental transmission of SARS-CoV-2 infection

Alexandre Vivanti
Paris Saclay University Hospitals
Chistelle Vauloup-Fellous
Paris Saclay University Hospitals
Sophie Prevot
Paris Saclay University Hospitals
Veronique Zupan
Paris Saclay University Hospitals
Cecile Suffee
Paris Saclay University Hospitals
Jeremy Do Cao
Paris Saclay University Hospitals
Alexandra Benachi
Paris Saclay University Hospitals
Daniele De Luca (dm.deluca@icloud.com)
Paris Saclay University Hospitals

Case Report

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Abstract

SARS-CoV-2 outbreak has spread and became the first pandemics of the century. SARS-CoV-2 infection is transmitted through droplets; other transmission routes have been hypothesized but never confirmed. So far, it has been unclear whether and how SARS-CoV-2 can be vertically transmitted from the mother to the fetus. We demonstrated for the first time the transplacental transmission of SARS-CoV-2 in a neonate born to mother infected in the last trimester. The transmission has been confirmed by a comprehensive virological study: SARS-CoV-2 transmission caused neonatal viremia placental inflammation which has been demonstrated by histological examination and immunohistochemistry. The neonate presented with neurological manifestation, consistent with those described in adult patients.

Introduction

SARS-CoV-2 infection causes the new coronavirus disease (COVID-19) and is mainly transmitted through droplets, but other transmission routes have been hypothesized. Some cases of perinatal transmission have been described,[1–6] but it is unclear if these occurred via the transplacental or the transcervical route or through environmental exposure. It is important to clarify whether and how SARS-CoV-2 reaches the fetus, so as to prevent neonatal infection, optimize pregnancy management and eventually better understand SARS-CoV-2 biology. Here we present a case study demonstrating, for the first time, the transplacental transmission of SARS-CoV-2.

Case Study

A 23-year-old, gravida 1, para 0 was admitted to our university hospital on March 24th, 2020 at 35^{+2} weeks of gestation with fever (38.6°C) and severe cough since March 22nd. Real-time polymerase chain reaction (RT-PCR) was performed as described in the **online methods:** both the E and S genes of SARS-CoV-2 were detected in blood, and in nasopharyngeal and vaginal swabs. Pregnancy was uneventful and all the ultrasound examinations and routine tests were normal until the diagnosis of COVID-19. Thrombocytopenia (54 x 10^9/L, normal range 140-400), lymphopenia (0.54 x 10^9/L, normal range 1-3.5), prolonged APTT (60 sec, normal range 28.0-41.9), transaminitis (AST 81 IU/L, normal range 13-37; ALT 41 IU/L, normal range 10-40), elevated C-reactive protein (37 mg/L, normal values <10) and ferritin (431 µg/L, normal range 7-191) were observed upon hospital admission. On March 27th, a category III-fetal heart rate tracing[7] (**Figure 1**) was observed and so category II-cesarean section was performed, with intact amniotic membranes, in full isolation and under general anesthesia due to maternal respiratory symptoms. Clear amniotic fluid was collected prior to rupture of membranes and during cesarean section and tested positive for both the E and S genes of SARS-CoV-2. Delayed cord clamping was not performed. The woman was discharged in good condition six days after delivery.

A male neonate was delivered (gestational age 35^{+5} weeks; birth weight 2540 grams) with Apgar scores of 4 and 2, at 1 and 5 minutes, and needed active resuscitation according to international guidelines[8] and

was eventually transferred in full isolation to the neonatal intensive care unit (NICU) in a negative pressure room. Cord blood gas analysis showed normal pH and lactate. Sarnat score, point-of-care echocardiography and lung ultrasound were normal upon NICU admission. Vital parameters were always normal and the baby was extubated after six hours. Before the extubation, blood was drawn for capillary blood gas analysis and routine blood tests which yielded normal values. Moreover, before the extubation, blood and non-bronchoscopic bronchoalveolar lavage fluid were collected for RT-PCR and both were positive for the E and S genes of SARS-CoV-2. Lavage was performed using a standardized procedure[9] as detailed in **online methods**. Nasopharyngeal and rectal swabs were first collected after having cleaned the baby at 1 hour of life, and then repeated at 3 and 18 days of postnatal age: they were tested with RT-PCR and were all positive for the two SARS-CoV-2 genes. Feeding was provided exclusively using formula milk.

On the second day of life, the neonate suddenly presented with irritability, axial hypertonia and opisthotonos: cerebrospinal fluid (CSF) was sterile but with 300 leukocytes/mm^3. Blood was taken at the same time: the culture was sterile and routine blood tests gave normal values. Cerebral ultrasound and EEG were also normal. Symptoms improved slowly over three days and a second CSF sample was normal on the fifth day of life, but mild hypotonia and feeding difficulty persisted. Magnetic resonance imaging at 11 days of life showed bilateral gliosis of the deep white periventricular and subcortical matter, with slightly left predominance (**Figure 2**). The neonate gradually recovered, feeding improved and was finally discharged from hospital after 18 days with an outpatient follow-up.

RT-PCR on the placenta was extremely positive for both SARS-CoV-2 genes. **Figure 3** shows all RT-PCR results obtained in different maternal and neonatal specimens. Placental histological examination was performed as described in **online methods** and revealed diffuse perivillous fibrin deposition with infarction and acute and chronic intervillositis. No pathogen agent was detected on special stains and immunohistochemistry performed. **Figure 4** depicts the results of the placental histological examination.

Discussion

We report the first proven case of transplacental transmission of SARS-CoV-2 from a pregnant woman affected by COVID-19 during late pregnancy to her offspring. Other cases of potential perinatal transmission have recently been described, but presented several unaddressed issues. For instance, some failed to detect SARS-CoV-2 in neonates or only reported the presence of specific antibodies;[1,2,4] others found the virus in the newborn samples but the transmission route was not clear as placenta, amniotic fluid and maternal or newborn blood were not tested.[3,5,6]

An international classification for the case definition of SARS-CoV-2 infection in pregnant women, fetuses and neonates has recently been released.[10] According to this classification system, a neonatal congenital infection is considered proven if the virus is detected in the amniotic fluid collected prior to the rupture of membranes or in blood drawn early in life, so our case fully qualifies as vertically transmitted SARS-CoV-2 infection, while the above would be classified as only possible or even unlikely.[10]

The placenta showed signs of inflammation consistent with the severe systemic maternal inflammatory status triggered by SARS-CoV-2 infection. As RT-PCR on the placental tissue was extremely positive for SARS-CoV-2, and both maternal and neonatal blood samples were also positive, the transmission clearly occurred through the placenta. Interestingly, placentas from women affected by SARS-CoV-1 presented similar pathological findings of intervillositis with intervillous fibrin deposition.[11] Angiotensin-converting enzyme 2 (ACE2) is known to be the receptor of SARS-CoV-2 and is highly expressed in placental tissues.[12] Animal data show that ACE2 expression changes in fetal/neonatal tissues over time and reaches a peak between the end of gestation and the first days of postnatal life.[12] The combination of these data and our findings confirms that transplacental transmission is indeed possible in the last weeks of pregnancy, although we cannot exclude a possible transmission and fetal consequences earlier during the pregnancy, as there are no literature data available yet.

Ours is also the first case of congenital infection presenting with neurological manifestations following neonatal viremia. Suspected neonatal SARS-CoV-2 infections presented with non-specific symptoms[4] or pneumonia,[3] while neurological symptoms are commonly observed in adult patients.[13] After the viremia, our case clearly presented neurological symptoms and inflammatory cells in CSF. There was no other viral or bacterial infection and other possible causes have been excluded. Neuroimaging consistently indicated white matter injury, which can be caused by the vascular inflammation induced by SARS-CoV-2 infection, as similar images have been anecdotally found in adult patients.[14,15] The combination of the clinical symptoms and history of this case qualifies for the diagnosis of neonatal COVID-19, according to the criteria suggested by Chinese colleagues.[16]

In conclusion, the vertical transmission of SARS-CoV-2 infection is possible through the placental route during the last weeks of pregnancy. Transplacental transmission may cause placental inflammation; neonatal viremia and neurological manifestations are also possible.

Declarations

AUTHORS' CONTRIBUTION

AV and CVF managed the mother and performed the whole virological study, performed the literature search, prepared the figures, interpreted the data and wrote the manuscript draft.

SP performed the pathological examination, prepared the figures and interpreted the data.

VZ and CS performed and interpreted the neuroimaging.

AB helped in literature search, data collection and interpretation and in the woman management.

DDL wrote the manuscript draft, managed the neonate, conceived the project and merged all the data.

All authors critically reviewed the manuscript for important intellectual content and approved it in its final version.

COMPETING INTERESTS

Authors have no conflict of interest to disclose

ETHICS DECLARATION

Written informed consent for publication of patient details was obtained from the patient

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

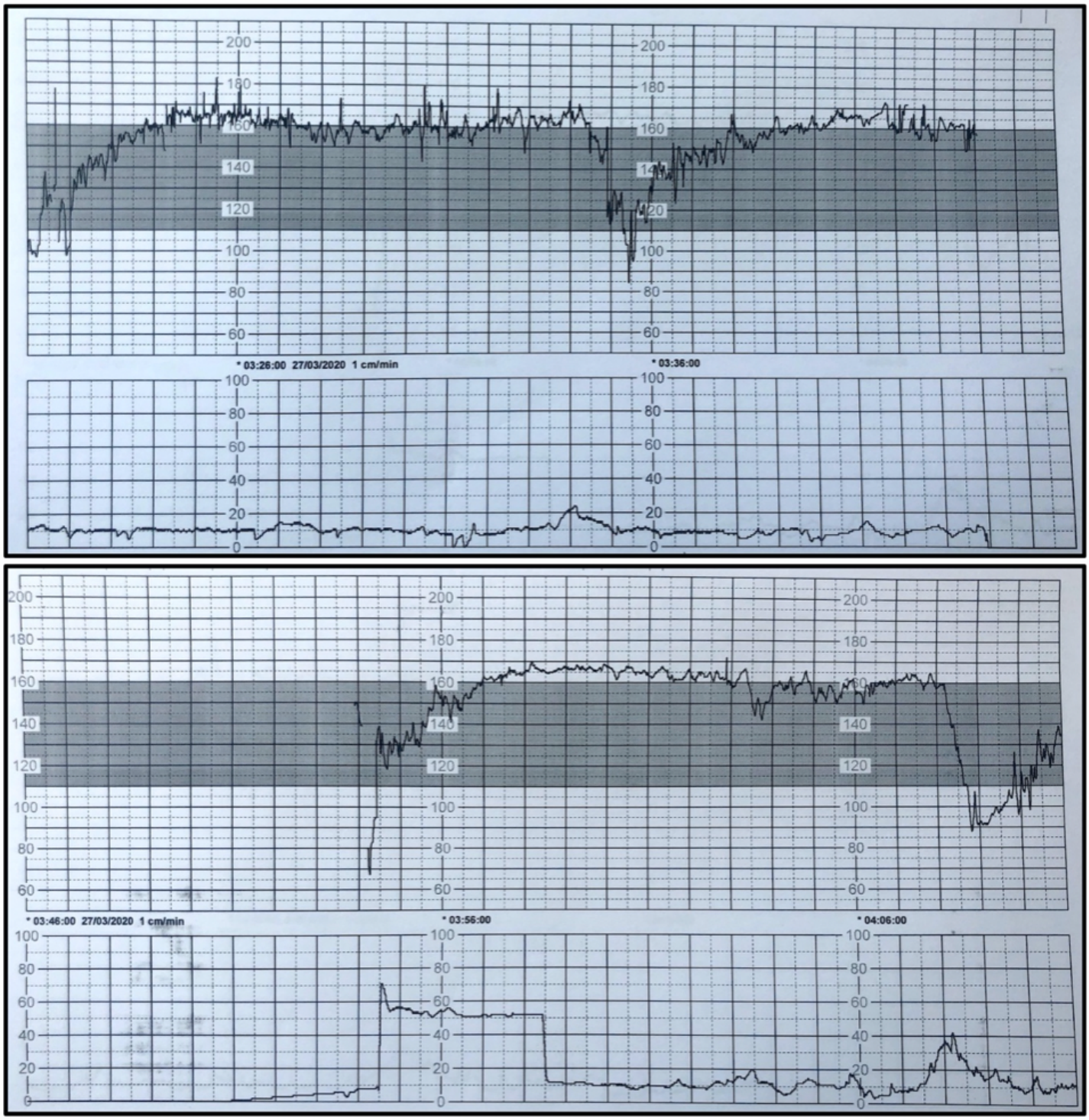

Figure 1

Fetal heart rate tracing. Tachycardia with recurrent prolonged and late decelerations highly suggestive of a pathological category III fetal heart rate tracing. This cardiotogram was recorded 26 minutes before the caesarean section.

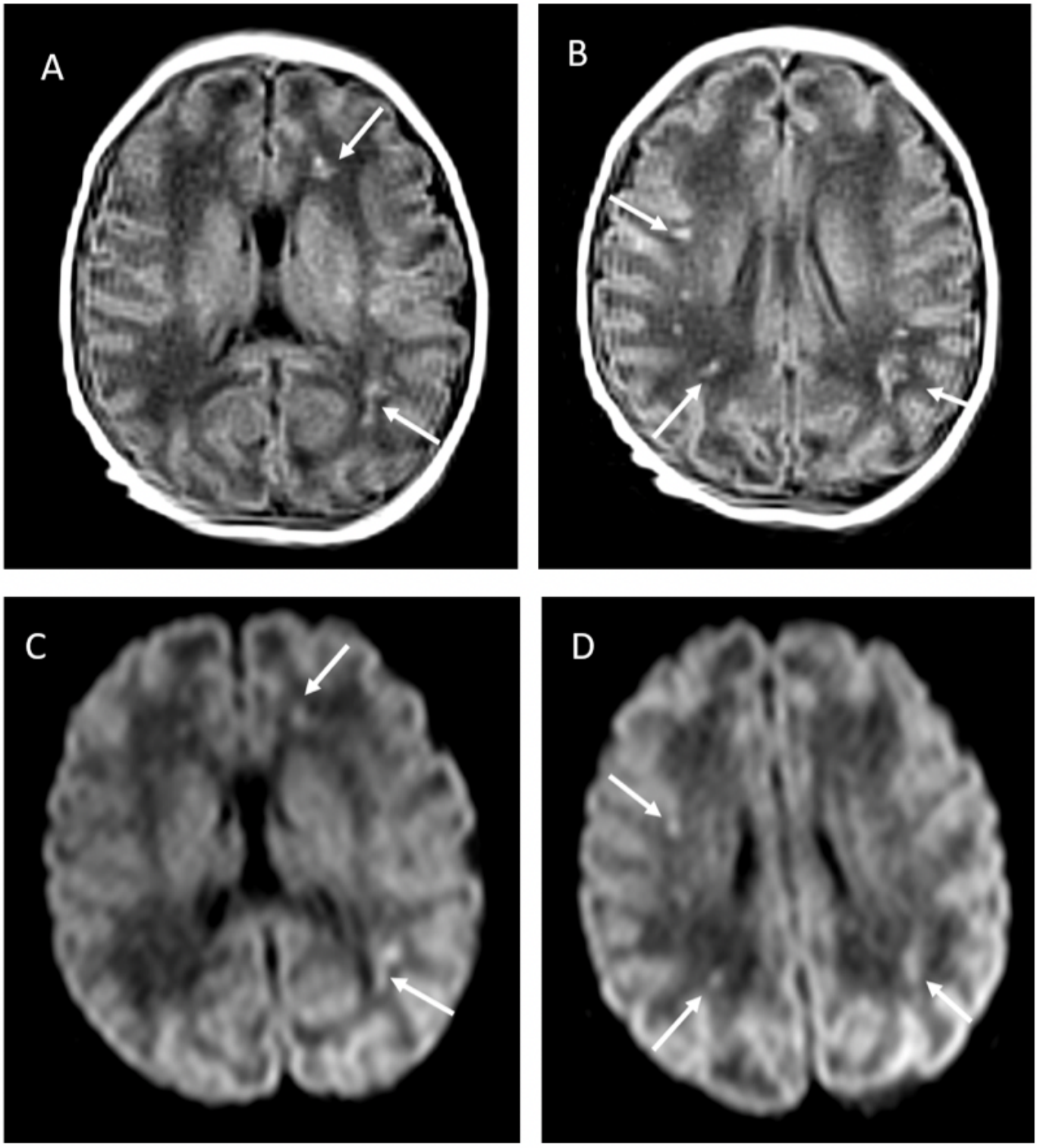

Figure 2

Cerebral MRI performed at 11 days of life. Panel A-B and C-D represents T1 and diffusion-weighted sequences, respectively. Images are taken at two different levels and show hyperintensities of the periventricular and subcortical frontal or parietal white matter (arrows).

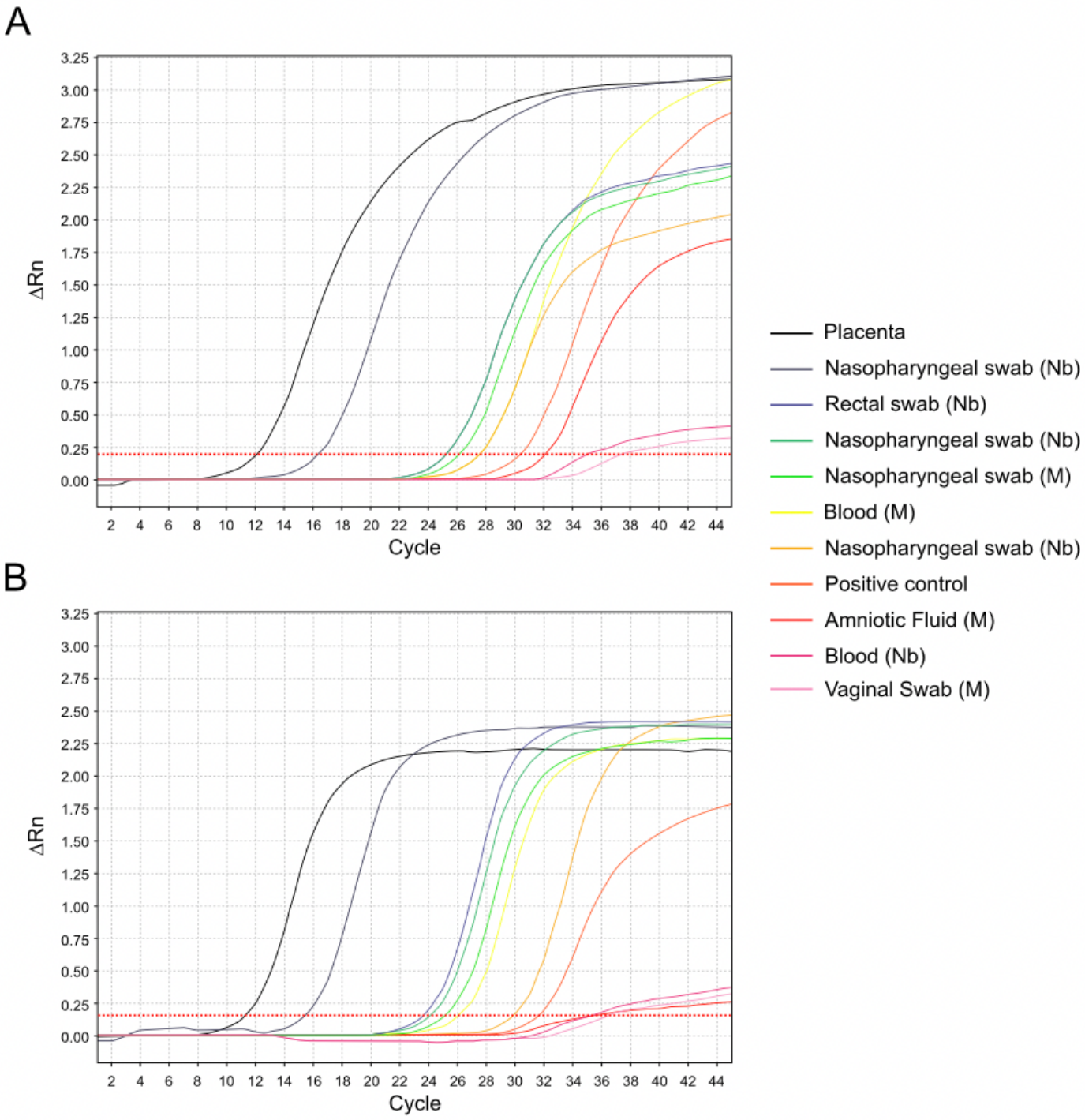

Figure 3

Real-time polymerase chain reaction results. Panels A and B show the E and S genes of SARS-CoV-2, respectively, for all maternal and neonatal samples. X and Y axes represent the amount of amplified RNA and the number of cycles, respectively. Colored lines represent the results of RT-PCR assay for each sample. Abbreviations: M: maternal samples; Nb: newborn samples.

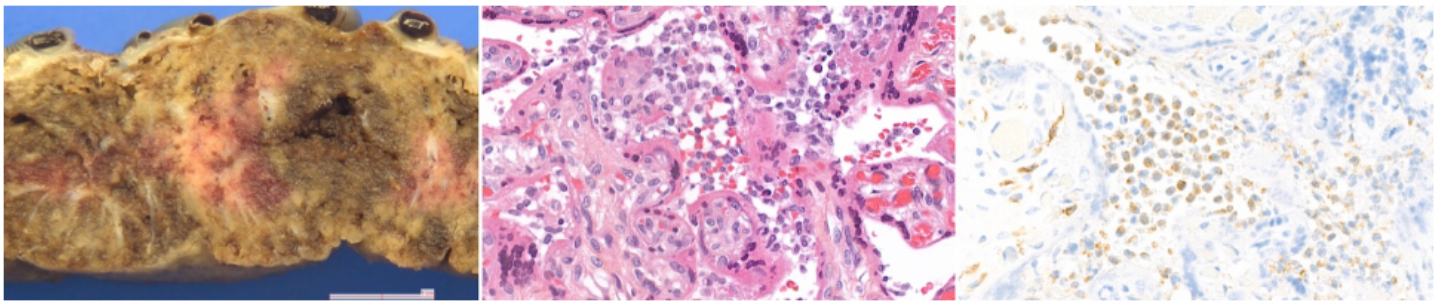

Figure 4

Histological examination of the placenta. Panel A illustrates the macroscopic examination, showing perivillous fibrin deposition with infarction (arrow). Panel B shows microscopic lesions of intervillositis (arrow) (HES stain, original magnification x400). Panel C shows the intervillositis with numerous CD68-positive histiocytes (arrow) (anti-CD68 immunohistochemistry, original magnification x400).

Supplementary Files

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