

Severe acute respiratory syndrome coronavirus 2 detected in placentas of 2 coronavirus disease 2019—positive asymptomatic pregnant women—case report



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There is limited evidence regarding severe acute respiratory syndrome coronavirus 2 infection in the placenta of pregnant women who tested positive, and if this could be a route for vertical transmission of the virus in utero. We present the cases of 2 pregnant women in their third trimester who were admitted for delivery by cesarean delivery and who, through universal screening, tested positive for coronavirus disease 2019. The maternal and fetal sides of the placenta were sectioned from both patients for viral analysis. Real-time polymerase chain reaction analysis of the placental-extracted RNA revealed a severe acute respiratory syndrome coronavirus 2 infection on the fetal side of the placenta in both patients. The virus was isolated from the patient with the lowest cycle threshold value on the fetal side of the placenta. Whole genome sequencing showed that the virus detected in this placenta was from the B1 lineage. Immunohistochemical analysis of the placental tissue detected severe acute respiratory syndrome coronavirus 2 in the endothelial cells of chorionic villi vessels proximal to both the maternal and fetal sides, with a granular cytoplasmic pattern and perinuclear reinforcement. Histologic examination of the placenta also detected a dense infiltrate of lymphoid cells around decidual vessels and endothelial cells with cytopathic changes, especially on the maternal side. Nasopharyngeal swabs from the infants that were subjected to reverse transcription quantitative polymerase chain reaction testing were negative for severe acute respiratory syndrome coronavirus 2 at 24 hours after birth. A follow-up analysis of the infants for immunoglobulin G and immunoglobulin M expression, clinical manifestations, and long-term developmental abnormalities is recommended.

Key words: case report, coronavirus disease 2019, pathologic effects, placenta, severe acute respiratory syndrome coronavirus 2, vertical transmission

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is a highly contagious viral agent that has infected a high proportion of pregnant women worldwide. Attention has been focused on determining whether the virus can be transmitted vertically to the fetus.

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AJOG MFM at a Glance

Why was this study conducted?

Vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the placenta and neonates from coronavirus disease 2019 (COVID-19)—positive mothers is a rare but possible event. The risk factors associated with this transmission are not completely understood and the pathologic effects of the infection on the placenta are still controversial. This study was conducted to evaluate if the circulating SARS-CoV-2 lineages are capable of infecting the placenta as a route of in utero vertical transmission and to describe its pathologic effects.

Key findings

We report on 2 clinical cases of SARS-CoV-2 placental infections in asymptomatic COVID-19—positive mothers in their third trimester of pregnancy, which resulted in neonates with SARS-CoV-2—negative nasopharyngeal swabs at 24 hours after birth. In the placenta, SARS-CoV-2 infection localized in granular patterns on the perinuclear region of the chorionic villi endothelial cells. A histologic examination also detected a dense infiltrate of lymphoid cells around decidual vessels and endothelial cells with cytopathic changes. The genetic characterization of the virus identified that 2 different lineages were implicated in these cases, namely the A2 lineage in case 1 and the B1 lineage in case 2. An a to g nucleotide mutation at position 23,403 (D614G) in the gene that encodes the viral spike protein, was observed in the sequence from the placental sample. A mutation previously considered to be a potential signal of adaptation by SARS-CoV-2, G11803T, was observed in both genomes.

What does this add to what is known?

Transmission of SARS-CoV-2 to the neonate has been reported mainly in pregnant women with a mild to critical COVID-19 status. Our finding supports the few reported cases of SARS-CoV-2 detection in the placenta of asymptomatic pregnant women. Previous studies have shown that COVID-19—positive neonates are mainly associated with the detection of SARS-CoV-2 in placental trophoblast cells. In this study, we present the histopathologic observations of SARS-CoV-2 in the perinuclear region of the chorionic villi endothelial cells in positive placentas that delivered COVID-19—negative neonates, supporting the hypothesis that the virus infection site in the placenta could play a role in the transmission to the neonate. Further studies are required to determine the route of transplacental mother-to-fetus transmission. In addition, our observed mutations of the virus detected in the placenta or the mother will need future analysis to determine if these are implicated in modulation of the viral capacity in placental infections.

Numerous placental samples from pregnant COVID-19—positive women have been analyzed and, from these, several cases of transplacental transmissions were described,^{1–14} which resulted in SARS-CoV-2—infected neonates.^{5–14} The risk factors associated with vertical transmission and the effects of SARS-CoV-2 infection on the placenta, which might influence the pregnancy and neonatal outcomes in infected women, are still not well understood. Here we report on 2 clinical cases of SARS-CoV-

2 placental infections with genetic characterization of the virus and a description of the pathologic effects observed in the infected placentas. By the time these cases were detected, Panama has reported more than 43,000 accumulated positive cases, including more than 400 infections in pregnant women.

Methods

Two pregnant women in their third trimester were admitted for delivery at

Hospital Santo Tomás in July 2020. Ethics review board approval (057-PCM-ICGES-20, EC-CNBI-2020-4-52) and written informed consent were obtained. Universal testing for SARS-CoV-2 viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR)¹⁵ from nasopharyngeal swabs of pregnant mothers before delivery was adopted by this hospital. The maternal and fetal sides of the placenta were collected for viral analysis and immunohistochemical staining as described in the [Supplemental Methods](#). Nasopharyngeal swabs from infants were taken 24 hours after delivery to determine the presence of SARS-CoV-2 by RT-qPCR.

CASE REPORT**Case 1**

A 23-year-old woman during her second pregnancy and without a marked medical history was admitted to the hospital owing to a bleeding placenta previa at 37 weeks of gestation ([Table](#)). She was hospitalized and a nasopharyngeal swab, which was used to test for the presence of SARS-CoV-2 2 days before the cesarean delivery, gave a positive result; however, the evolution of the SARS-CoV-2 infection was asymptomatic. SARS-CoV-2 viral RNA was detected on the fetal side of the placenta with a cycle threshold (Ct) value of 31 ([Table](#)). Viral isolation and whole genome sequencing from the placenta were not successful, consistent with previous studies, showing that viral particles from samples with a Ct value of >29 are difficult to isolate and sequence.¹⁶ However, the virus was successfully sequenced from the nasopharyngeal swab of the mother. The whole genome indicated that the virus was from the A2 lineage, the main lineage circulating in Panama¹⁷ ([Figure 1](#)). A histopathologic examination of the maternal side of the placenta showed hemorrhagic necrosis and hematomas with no inflammatory cell infiltration. The chorionic villi were small for gestational age ([Figure 2, A and B](#)). The villous stem vessels were sclerotic with smooth muscle hyperplasia and fibrin deposition, consistent with chronic hypoxia ([Figure 2, C](#)). Immunohistochemical analysis for SARS-CoV-2 showed

TABLE
SARS-CoV-2 detection in the placenta of 2 patients with COVID-19

Patient number	Age	Gestational age at admission	Gestational age at delivery	Interval from detection of SARS-CoV-2 and delivery (d)	COVID-19 symptoms	Delivery method	PCR of placenta sample (Ct value)	Viral isolation from placenta	PCR of infants nasopharyngeal swabs (within 24 h birth)
1	23	37	37	2	Asymptomatic	Cesarean delivery	31	Negative	Negative
2	21	36	37	1	Asymptomatic	Cesarean delivery	22	Positive	Negative

COVID-19, coronavirus disease 2019; Ct, threshold cycle; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Sanchez. Severe acute respiratory syndrome coronavirus 2 detected in placenta. Am J Obstet Gynecol Glob Rep 2021.

granular cytoplasmic patterns in the endothelial cells from the chorionic villi vessels in proximity to the maternal and fetal side with perinuclear reinforcement (Figure 2, D–F), a pattern not observed in the negative control (Supplemental Figure 1). The trophoblast cells were negative for SARS-CoV-2 expression. Overall, the chorionic villi vessels showed hyperplasia with no cytopathic effects nor inflammation within the stromal tissue. The newborn showed normal developmental manifestations, with a weight of 2550 grams, and an Apgar score of 9 at 1 and 5 minutes. A nasopharyngeal swab was collected from the neonate 24 hours after birth and tested negative for SARS-CoV-2.

Case 2

A 21-year-old woman, during her first pregnancy, with chronic renal failure and a history of treated syphilis was admitted to the hospital at 36 weeks of gestation owing to preeclampsia. Conservative management was provided until the 37th week of gestation, at which time labor was induced. A nasopharyngeal swab was performed 1 day before delivery, which tested positive for SARS-CoV-2. During the active phase of labor, because of a category 2 fetal heart rate with recurrent late decelerations, a cesarean delivery was performed. The incidence of preeclampsia was not attributed to COVID-19 because the patient was diagnosed with preeclampsia 1 week before the delivery and was asymptomatic. SARS-CoV-2 viral RNA was detected on the fetal side of the placenta with a Ct value of 22 (Table). Viral isolation from the placenta was successful, showing that the detected SARS-CoV-2 was infectious. SARS-CoV-2 on the maternal side of the placenta had a cytopathic effect on Vero cells, however, the viral levels were too low for detection by RT-qPCR. The whole viral genome obtained from the fetal side of the placenta indicated that the SARS-CoV-2 identified was from the B1 lineage (Figure 1). The quantity of the viral RNA in the nasopharyngeal swab of the mother was not enough to successfully sequence the whole genome. The SARS-CoV-2 genome

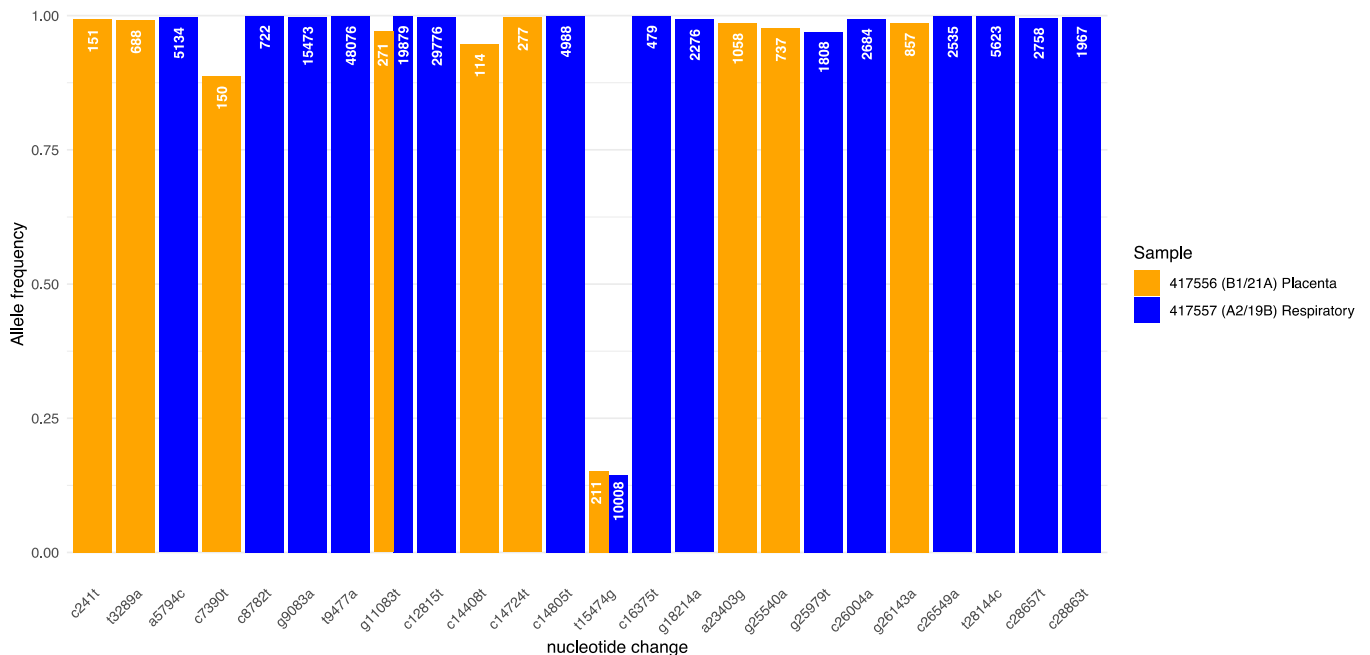
sequenced from the mother's respiratory sample in case 1 (lineage A2) was compared with the sequence obtained from the fetal side of the placenta in case 2 (lineage B1). Both had similar nucleotide changes when compared with the MN908947 reference genome (Figure 1). A nucleotide mutation, an a to g at position 23,403 (D614G), in the gene that encodes the spike protein variant (614G)¹⁸ was observed in the viral genome from the placenta. The nucleotide mutation G11803T was observed in both genomes.

Placental histologic evaluation on the maternal side showed lymphocyte infiltration, which surrounded the decidual vessels and endothelial cells, in addition to cytopathic changes such as karyomegaly and hyperchromia (Figure 3, A). The changes in the chorionic villi adjacent to the decidual tissue were consistent with chronic hypoxia, which included stromal sclerosis, fibrin deposits, vascular proliferation of the stem villus vessels, and syncytial knots, but no inflammatory changes were observed (Figure 3, B and C). The chorionic membrane on the fetal side of the placenta did not show any inflammatory cells nor changes that may suggest cellular lesions. Immunohistochemical analysis for SARS-CoV-2 showed granular cytoplasmic patterns in the endothelial cells from the chorionic villi vessels in proximity to the maternal side with perinuclear reinforcement (Figure 3, D and E; Supplemental Figure 2). The trophoblast cells were negative for SARS-CoV-2 expression. Stronger staining for SARS-CoV-2 was observed in the chorionic vessels near the maternal side, although similar patterns were observed in the chorionic vessels near the fetal side (Figure 3, F). The neonate was normal with a weight of 2890 grams, and an Apgar score of 9 at 1 and 5 minutes. A nasopharyngeal swab was negative for SARS-CoV-2 within 24 hours of age.

COMMENT

We presented 2 cases of asymptomatic COVID-19—positive pregnant women with detection of SARS-CoV-2 in the endothelial cells from the chorionic villi in the placenta, but both with negative

FIGURE 1
Nucleotide variants found in the SARS-CoV-2 genomes analyzed



The number of reads in each position is shown in the bars. Only variants with more than 10% of depth are shown; positions are based on the MN908947 reference genome. Blue bars, genome from the respiratory sample of case 1; Yellow bars, genome from the placental fetal side of case 2.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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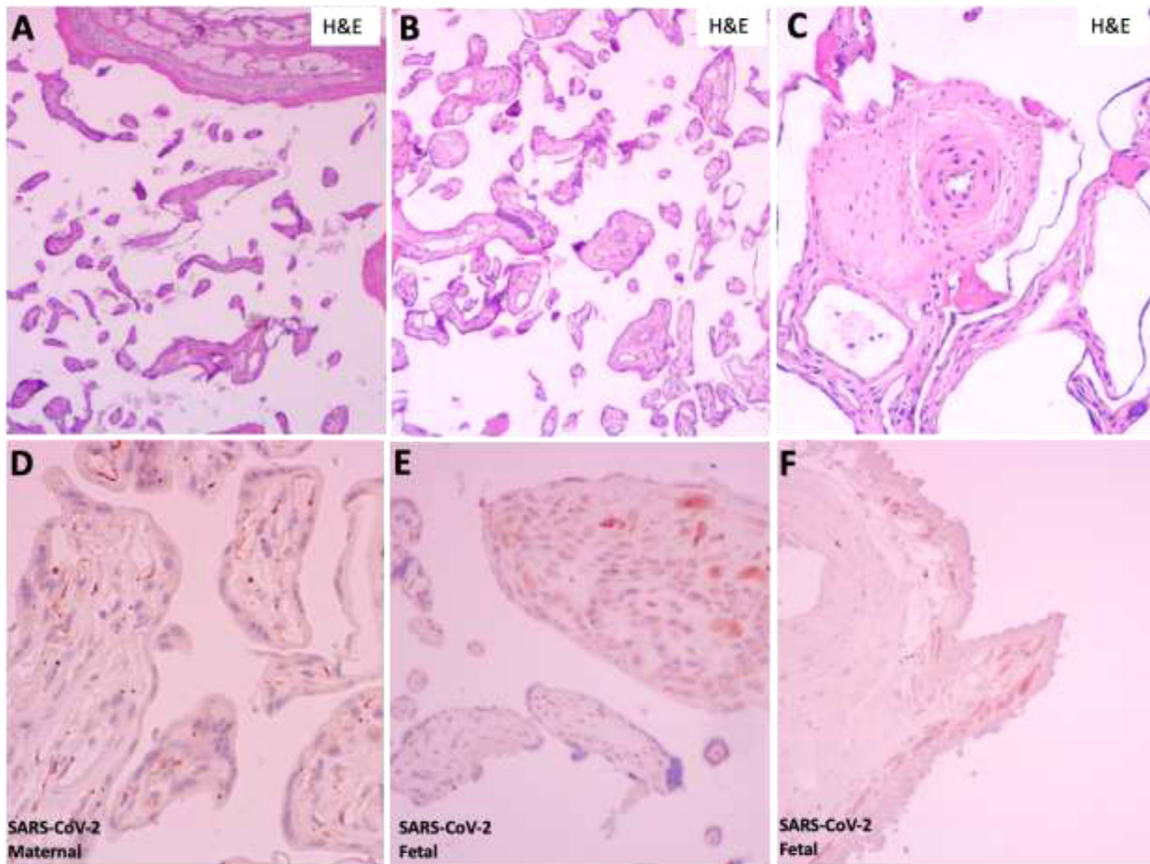
neonates. Transmission of SARS-CoV-2 to the neonate has been reported mainly in pregnant women with a mild to critical COVID-19 status. Thus far, only a few cases of SARS-CoV-2 detection in the placenta of asymptomatic pregnant women have been reported.³ Interestingly, vertical transmission of SARS-CoV-2 to the neonate from asymptomatic mothers has not been reported yet, which is consistent with our results. A correlation between the COVID-19 status in pregnant women and the vertical transmission of SARS-CoV-2 still needs to be identified.

We were able to successfully isolate and sequence the whole genome of SARS-CoV-2 from the placenta in 1 case, possibly because of the higher viral presence. At the time of detection, the lineages in case 1 (A2) and case 2 (B1) had a local prevalence of around 53.4% and 14.4%, respectively.¹⁷ Further studies should be

done in pregnant women to determine the possible association between specific lineages and vertical transmission, and to evaluate whether the A23403G (D614G)¹⁸ and G11803T¹⁹ mutations, both potential signals of viral adaptation, are associated with a viral mechanism for vertical transplacental transmission.

Histologic evaluation of the placenta showed sclerotic chorionic villi and other pathologic effects consistent with chronic hypoxia.³ In contrast to other studies,^{1,12,13} we did not detect inflammatory infiltration. On the maternal side, we observed lymphocyte infiltrations surrounding the endothelial cells, which presented with cytopathic effects. Our results support previous observations that suggested a possible association between SARS-CoV-2 infections in placental syncytiotrophoblast cells in villi and vertical transmission that resulted in COVID-19-positive

newborns,^{12–14} whereas when SARS-CoV-2 infected the endothelial cells of the chorionic villi, as observed in these 2 cases, no transmission to the newborn was detected.¹² Studies have reported that the expression levels of the SARS-CoV-2 receptors, angiotensin-converting enzyme 2 and transmembrane serine protease 2, in the placenta exhibited a negative correlation with gestational age, suggesting a reduced likelihood of viral entry during later stages of pregnancy.²⁰ However, consistent with our results, SARS-CoV-2 has been detected in third-trimester placentas,^{1–3,5–14} suggesting that the low quantity of receptors present during the later stages might be sufficient for placental infection, but too low for vertical transmission.²¹ Further studies with infected mothers are required to correlate SARS-CoV-2 receptors expression levels with transplacental transmission to the neonate.

FIGURE 2**Immunohistochemical evaluation of the SARS-CoV-2–positive placenta of case 1**

A, Decidua with small and sclerotic chorionic villi; H&E stain, 40 × magnification; **B**, Small and sclerotic chorionic villi; H&E stain, 40 × magnification; **C**, Chorionic villus with a hyperplastic and sclerotic blood vessel; H&E stain, 100 × magnification; **D**, Chorionic villi near the maternal side; IHC anti–SARS-CoV-2, 100 × magnification; **E**, Chorion with chorionic villi near fetal side; IHC anti–SARS-CoV-2, 40 × magnification; **F**, Chorionic plate near the fetal side; IHC anti–SARS-CoV-2, 40 × magnification.

H&E, hematoxylin and eosin; IHC, immunohistochemistry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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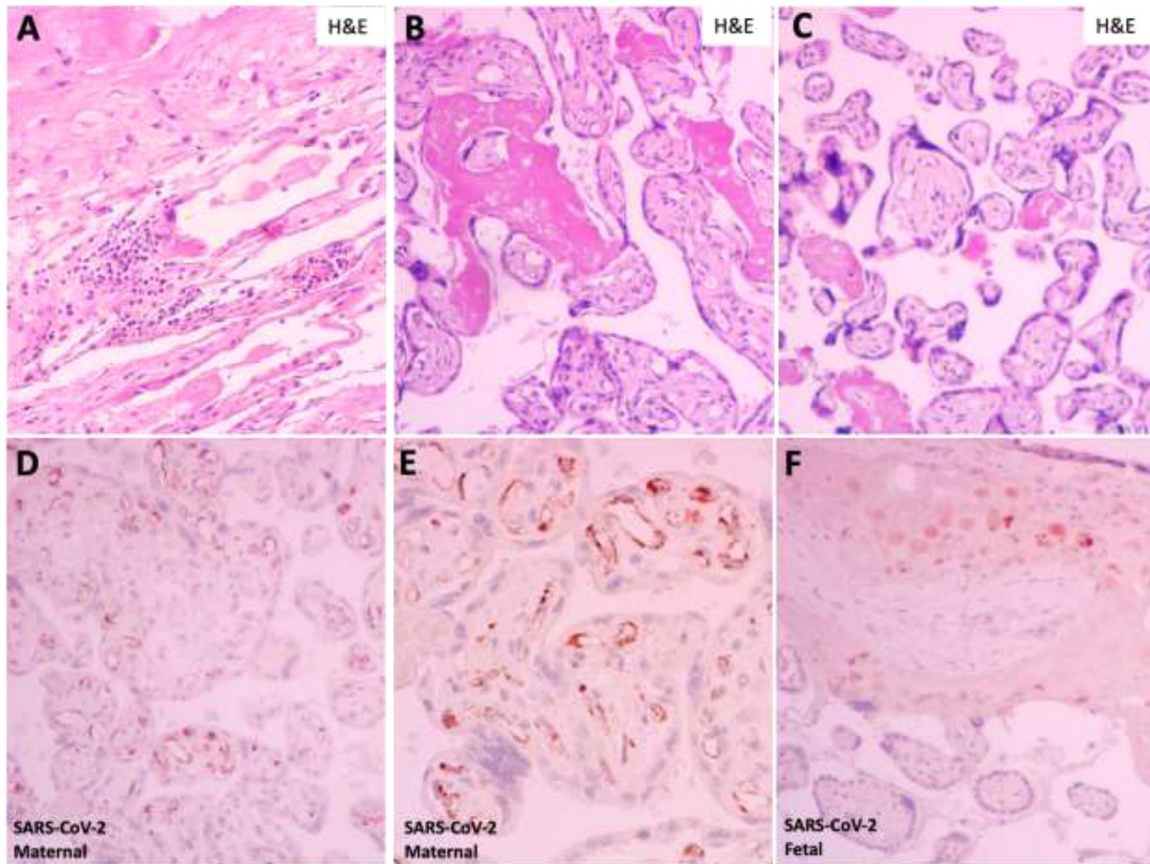
The newborns had negative results for COVID-19 from nasopharyngeal swabs obtained 24 hours after birth, and both remained asymptomatic. SARS-CoV-2 in neonates delivered from COVID-19–positive mothers has been detected as early as 1 hour after birth, and stayed positive even after 18 days.¹⁰ Thus, we strongly recommend that

repeated RT-qPCRs on days 3 and 5 after birth, along with SARS-CoV-2 serologic immunoglobulin tests, should be performed to validate the negative results. Further follow-ups of the infants born from SARS-CoV-2–positive mothers is needed to determine if SARS-CoV-2 infection during pregnancy and the pathologic effects

observed in the placenta could have repercussions on the development of the neonate, even in the absence of mother-to-fetus vertical transmission.

This report shows the need for the implementation of a global surveillance for pregnant women and neonates during the COVID-19 pandemic and also for future emergent pathogens. ■

FIGURE 3
Immunohistochemical evaluation of the SARS-CoV-2–positive placenta from case 2



A, Perivascular lymphocytic infiltrate in the decidual blood vessels; H&E stain, 40 × magnification; **B**, Chorionic villi with intervillous fibrin deposition; H&E stain, 100 × magnification; **C**, Syncytial knots; H&E stain, 100 ×; **D**, Chorionic villi near the maternal side; IHC anti–SARS-CoV-2, 40 × magnification; **E**, Chorion with chorionic villi near the fetal side; IHC anti–SARS-CoV-2, 100 × magnification; **F**, Chorionic plate without amnion near the fetal side; IHC anti–SARS-CoV-2, 40 × magnification.

H&E, hematoxylin and eosin; IHC, immunohistochemistry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.xagr.2020.100001](https://doi.org/10.1016/j.xagr.2020.100001).

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