Finding of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Within Placental Tissue 11 Weeks After Maternal Infection

To the Editor.—We read with particular attention the article of Schwartz et al1 recently published in your journal. We want to discuss a case of long persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in placental specimens, associated with histiocytic intervillositis, marked increase in perivillous fibrin deposition, and chronic high-grade villitis. The mother was previously hospitalized for a symptomatic SARS-CoV-2 infection at gestational week (GW) 26, and spontaneous delivery occurred at GW 37. The reverse transcription polymerase chain reaction result of the nasopharyngeal swab taken at delivery was negative in both mother and child. Placental weight was less than the third centile for gestational age, no intrauterine growth restriction was recorded during pregnancy, and the neonatal outcome was unremarkable.

Here we show a pattern of histiocytic intervillositis associated with the immunohistochemical permanence of SARS-CoV-2 in Hofbauer cells and in the walls of intravillous fetal vessels (hematoxylin-eosin, original magnifications ×20 [A] and ×25 [B]; PGM1 ready-to-use, DAKO, original magnification ×25 [C]; anti-nucleocapsid, original magnification ×40 [D]).

Viruses can be vertically transmitted from mother to infant through intrauterine (hematogenous or ascending paths), intrapartum, and postpartum routes. Even though a large majority of infants born to pregnant women with coronavirus disease 2019 (COVID-19) have been uninfected, new evidence shows that vertical transmission can occur. A recent analysis revealed that nearly 70% of SARS-CoV-2–positive neonates acquired the infection through postpartum transmission, with the remaining 30% through intrauterine or intrapartum mechanisms. Among all (122), 5.7% were stated to have confirmed congenital infection.2 It has been reported that, once the transmission has taken place, its effect on the fetus and the newborn can be relevant, leading to preterm delivery, admission to neonatal intensive care, or even stillbirth. A review of literature has shown only a case of persistence of the virus associated with placental lesions suggestive of inflammation after a previous SARS-CoV-2 infection. However, in this case, the infection occurred at GW 8, leading to a spontaneous abortion at GW 13.3 Although the placental lesions previously described in the work of Schwartz et al1 were related to an acute, symptomatic infection, here we demonstrate a histiocytic intervillositis with specific viral persistence, even after 11 weeks from the previous maternal symptomatic infection, in an otherwise healthy mother and newborn.

All these findings may be the consequence of an immune-mediated persistent injury to the maternal-fetal...
interface. Trophoblast destruction may act as a potential mechanism to allow the virus to penetrate the chorionic villi and, once it has reached the fetal vessels, to become widespread in the fetal circulation, persisting in fetal vessels and macrophages, as shown (Figure, D).

Besides confirming the pathogenesis of damage previously hypothesized, our findings add new relevant information about how long SARS-CoV-2 can survive in human placentas. This may be crucial for clarifying the viral mechanism of persistence in all the tissue involved after primary infection, not only in trophoblastic-derived cells.

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In Reply.—I was very pleased to read the Letter to the Editor by Toto et al in response to our recent article.1 Their description of an 11-week interval between the initial confirmed maternal coronavirus disease 2019 (COVID-19) infection and delivery in which the placenta was found to have immunohistochemical evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleocapsid protein staining is interesting. It is noteworthy that although active inflammatory abnormalities were present—chronic histiocytic intervillositis and chronic villitis—the syncytiotrophoblast did not show evidence of SARS-CoV-2 immunohistochemically staining at this stage, with positivity limited to villous stromal macrophages (Hofbauer cells) and capillary endothelium. This staining pattern is especially interesting as the susceptibility and kinetics of SARS-CoV-2 viral infection in the constituent cells of the maternal-fetal interface are currently unknown. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (TMPRSS2) for cell entry. Syncytiotrophoblast and vascular endothelial cells express ACE2,2,3 while syncytiotrophoblast expression of TMPRSS2 has been reported in some studies4 but not others. Hofbauer cells, which stained positively for SARS-CoV-2 nucleocapsid protein in this Letter to the Editor, do not appear to have the ACE2 surface receptor for SARS-CoV-2 binding.2,3 and also appear to lack TMPRSS2.2 Perhaps this case represents the opportunity to view the natural history of prolonged placental infection due to SARS-CoV-2, as previously published cases of maternal and placental infection have occurred more proximate to delivery. It is also notable that despite the pathology findings and prior symptomatic maternal infection, the newborn tested negative for SARS-CoV-2.

This report also suggests at least 2 potential possibilities to explain the clinical and pathologic findings. The placenta has multiple innate immune mechanisms to protect the fetus from infection: these include production of antiviral molecules that can inhibit viral infections; pattern recognition receptors including Toll-like receptors and RIG-I-like receptors that induce antimicrobial signaling pathways; production of type III interferons (IFN-λs) and C19MC microRNAs that restrict viral infections; active transport of antibodies to the fetus through expression of IgG (immunoglobulin G) receptors neonatal FcRn and FcγRIII that are present on the syncytiotrophoblast surface; and physical structure of the syncytiotrophoblastic barrier. Placental macrophages at the maternal-fetal interface, such as Hofbauer cells, may also potentially have antimicrobial functions in SARS-CoV-2 infection, although this remains unknown.5 Perhaps these and other factors were sufficient in this case to prevent fetal infection despite placental involvement. Alternatively, given the 11-week interval between maternal infection and delivery, is it possible that the fetus became infected with SARS-CoV-2 following transplacental transmission, but subsequent clearing the coronavirus before delivery? It has been noted that neonatal test positivity for SARS-CoV-2 is frequently transient, becoming negative in many newborn infants a short time following a positive result.7,8 As is occurring with so many communications in obstetric, placental, and perinatal COVID-19, this thought-provoking report introduces more questions than it answers in our attempts to understand the pathophysiology of this emergent coronavirus infection during pregnancy.

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