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# Authors' response to "Response to Diffuse Trophoblast Damage is the Hallmark of SARS-CoV-2-associated fetal demise"



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**TO THE EDITOR:**

We appreciate the interest of Drs Torous, Watkins, and Roberts in our publication "Diffuse trophoblast damage is the hallmark of SARS-CoV-2-associated fetal demise" where we analyzed the histologic lesions in placentas infected by SARS-CoV-2 as detected by RT-PCR, immunohistochemistry, and in situ hybridization[1]. We see the point they make and we can partially agree with them. According to our findings, SARS-CoV-2 placental infection can occur in a focal or a diffuse pattern. Focal lesions mimic villous infarction, they are discrete lesions that can be macroscopically measured, and they occur in placentas from mothers that were positive at some time during pregnancy but they were no longer positive at delivery (cases #8 and #9). Diffuse lesions (not directed towards one place or concentrated in one place but spread out over a large area) occur in women SARS-CoV-2-positive at delivery but vary in the volume of tissue actually involved. Cases with limited involvement (20% of placenta -case #4- or only detected microscopically -case #6) resulted in livebirths. Fetal demises occurred only among cases with a diffuse pattern and a massive involvement (80% or more of placental tissue; cases #1, #2, #3, #5, and #7) suggesting that placental insufficiency depends on the amount of affected tissue. The term "massive" could more precisely depict the kind of involvement associated with fetal demise but we chose "diffuse" trying to make a parallelism with Diffuse Alveolar Damage, the suggested initial lung injury in cases of fatal COVID-19 pneumonia that shares a similar gene expression profile with SARS-CoV-2 infected placentas[1–3]. We would like to point out that the actual amount of placental tissue involved estimated at gross inspection is only seldomly reported. Among the reports that include this estimation, fetal demise is only reported among cases with 70% or more of placental involvement[1,4–8]. Some surviving babies with such extensive placental involvement had their pregnancies terminated by cesarean section or induction of delivery because either pathologic fetal heart rate or Doppler ultrasound anomalies[5]. These findings support our conclusions: fetal death occurs only among cases with extensive placental lesions. Unfortunately, most of reports do not include a precise macroscopic description, and some attempt to estimate this involvement according to the extent of lesions seen in histologic slides. Caution must be taken when this method is used, because in diffuse lesions, histologic sections are likely selected in the most affected areas, therefore overestimating the actual extent.

We dislike the term "placentitis" to describe the constellation of histologic alterations of SARS-CoV-2 placental infection that include trophoblast necrosis with intervillous space collapse, histiocytic intervillitis, and fibrin(oid) deposition. Placentitis was used to describe histologic alterations in TORCH infections. These are usually chronic infections characterized by chronic villitis that sometimes result in necrosis mainly in the villous stroma with occasional trophoblast lining involvement. Neither trophoblast necrosis, nor histiocytic intervillitis nor fibrin(oid) deposition are characteristic of TORCH placentitis. We fear that the denomination of "placentitis" can mislead pathologists and clinicians to investigate for other TORCH infectious agents in cases of SARS-CoV-2 infection. We suggest "trophoblastic damage" as others[1,9] because we consider trophoblast necrosis as the primary lesion

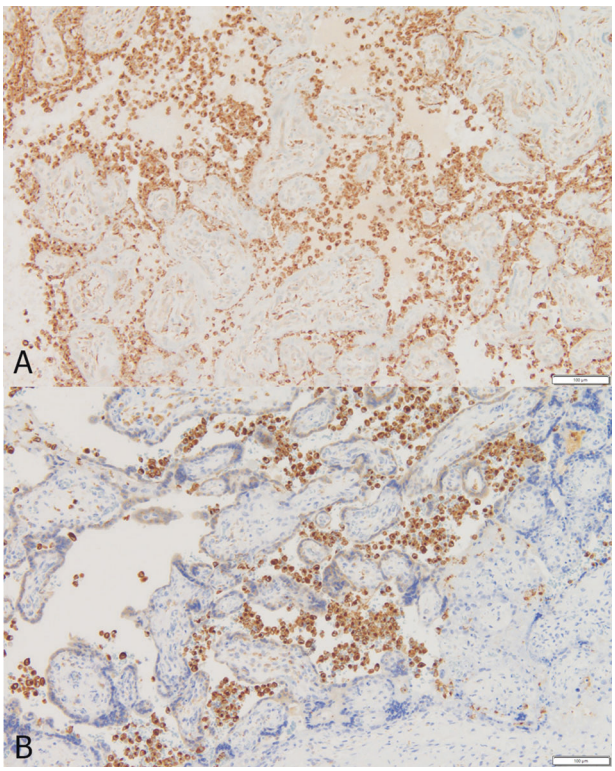


**Fig. 1 SARS-CoV-2-related and SARS-CoV-2-unrelated intervillitis.** Intervillous inflammatory component in SARS-CoV-2-infected placentas shows a pattern of perivillitis outlining the villi contour (**A**) whereas in classical chronic histiocytic intervillitis the inflammation preserves the trophoblast lining (**B**). CD68 immunohistochemistry, original magnification 10×.

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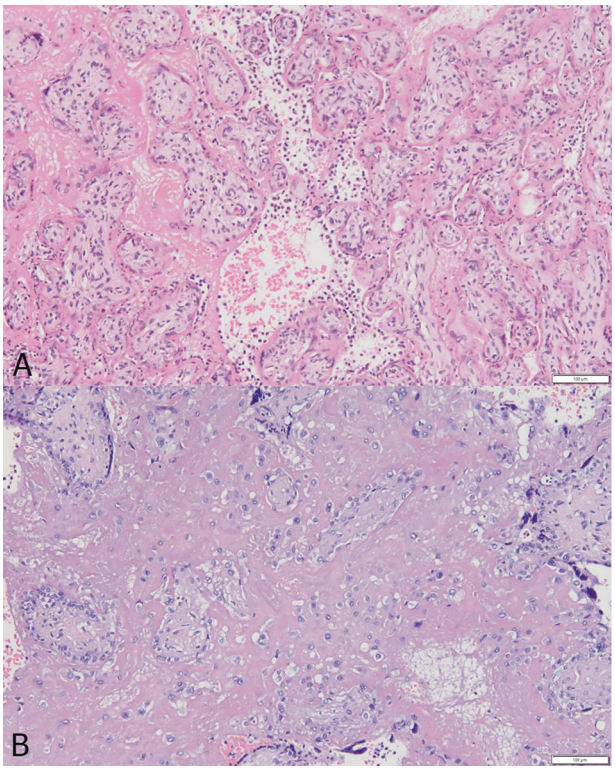


**Fig. 2 Comparison between SARS-CoV- 2-related trophoblast necrosis and typical massive fibrin(oid) deposition.** Trophoblast necrosis with intervillous space collapse showing crowding of villi (**A**) versus perivillous fibrin(oid) deposition (**B**) where villi are separated from each other by the fibrin(oid) deposition resulting in less villi per area. H&E, original magnification 10×.

derived from SARS-CoV-2 placental infection. Although different reports identify the virus in a variety of cell types, trophoblast infection is identified in all analyzed cases. Our findings point to trophoblast infection and subsequent trophoblast necrosis as the primary lesion in these placentas. Quantification of the different components of the lesions results in a striking predominance of the trophoblast necrosis which is present in 65 to 97% of the injured tissue area. It clearly outnumbers the other components: histiocytic intervillitis can be seen in 34 to 50% of the injured tissue and increased fibrin(oid) deposition is present in 10 to 45% of tissue. With these figures, trophoblast necrosis is the only lesion seen alone in extensive areas, whereas both histiocytic intervillitis and fibrin(oid) deposition were usually merged with trophoblast necrosis.

We would like to take the opportunity to make some comments about intervillitis and fibrin(oid) deposition in SARS-CoV-2 placental infection. We disagree with reports that describe the inflammatory response as "chronic histiocytic intervillits", because the clinical course of SARS-CoV-2 infection is acute. Most of reported cases had the first evidence of maternal infection close to delivery, usually within two weeks time, and there is a neutrophilic component added to the histiocytic and, to a lesser degree, the lymphocytic component. Both elements, clinical course and histologic composition, support an acute nature of the process (Fig. 1). Similarly, the fibrin(oid) deposition seen in SARS-CoV-2-infected placentas is rarely continuous from chorionic to basal plate and is usually restricted to less than 50% of the villi in a single slide (Fig. 2). These two lesions are associated with intrauterine growth restriction, an infrequent condition among SARS-CoV-2-infected placentas. Thus, neither histiocytic intervillitis nor fibrin(oid) deposition in SARS-CoV-2-infected placentas fit the canonical descriptions or clinical characteristics of "chronic histiocytic intervillitis" and "massive perivillous fibrin(oid) deposition", then we discourage the use of these terms in the description of these placentas.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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