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TITLE PAGE

Ultrastructural evidence for vertical transmission of SARS-CoV2.

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HIGHLIGHTS

- SARS-CoV-2 virions identified by transmission electron microscopy in placenta
- Mother, neonate and placental tissue COVID-positive by molecular testing
- Ultrastructural evidence supporting molecular evidence for vertical transmission

Keywords: electron microscopy, SARS-CoV-2, placenta, vertical transmission

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Since the initial *Lancet* correspondence by Goldsmith et al. (2020), there have been numerous published electron micrographs of putative SARS-CoV-2 virions in biopsy and autopsy tissues. A recent review of these images (Bullock et al., 2021) indicated that previous ultrastructural reports of virions in placental tissue, were mis-identifications. Placental histology of mothers and neonates both testing positive for SARS-CoV-2, is typified by chronic histiocytic intervillitis and trophoblast necrosis, with RNA in situ hybridization/immuno-histochemical findings localising viral RNA/viral antigens to the syncytiotrophoblast (Schwartz and Morotti, 2020). This histopathology is considered a risk factor for vertical transmission of SARS-CoV-2, which, as yet, is infrequently documented (Bukowska-Osko et al., 2021).

Ten days prior to a caesarean section performed at 30 weeks due to decreased fetal movements, a mother tested positive for SARS-CoV-2 by routine PCR. The neonate tested positive for the virus by rectal swab, two days after delivery. Histology of the formalin-fixed placental tissue showed high grade lymphohistiocytic villitis with extensive histiocytic (CD68- positive) intervillitis with massive perivillous fibrin deposition (+/-60% of the placental parenchyma), low grade fetal vascular malperfusion, and diffuse villous oedema. RNA was extracted from a section of formalin-fixed placental tissue using the Promega Maxwell® 16 System. The extract tested positive for SARS-CoV-2 using the Applied Biosystems™ TaqPath™ COVID-19 CE-IVD RT-PCR assay. The Ct values obtained for each gene were N=28.65, S=29.25 and Orf1=27.45. Transmission electron microscopy of the formalin-fixed tissue revealed the

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presence of *Coronavirus* particles in membranous vacuoles within the syncytiotrophoblast, thus providing ultrastructural evidence of vertical transmission.

Ethical approval: Ethical approval was not required.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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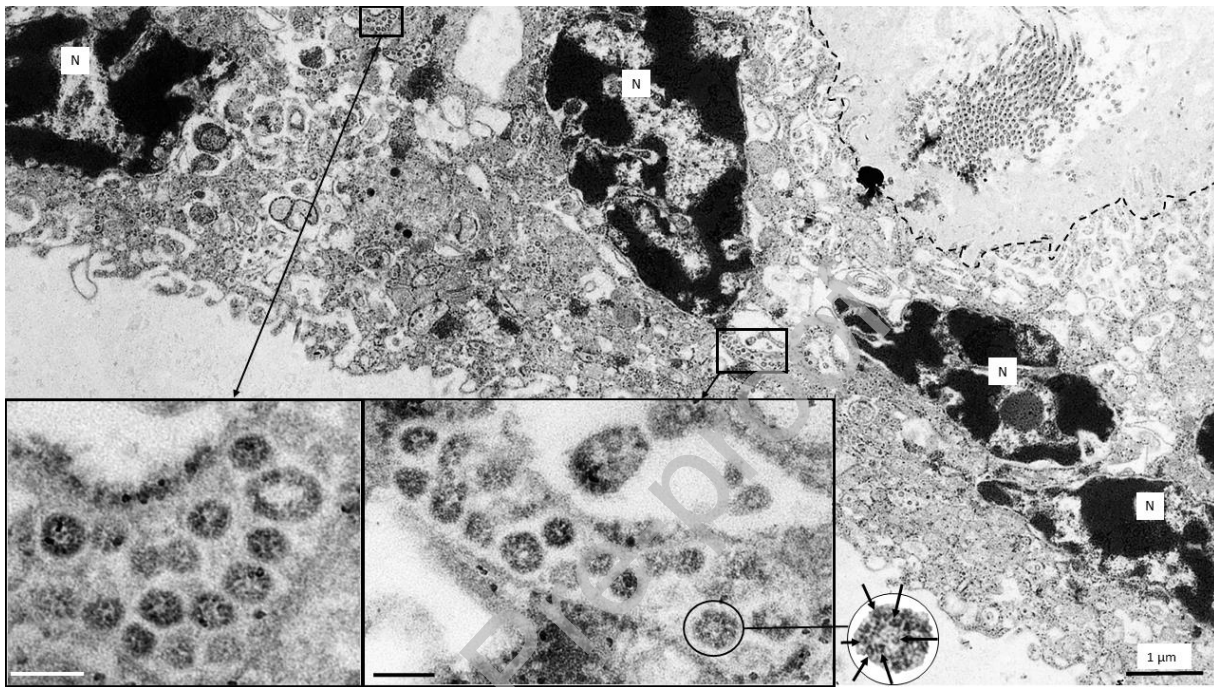


Figure: SARS-CoV-2 infected placental tissue

The cytoplasm of the multinucleate placental syncytiotrophoblast was found to contain numerous vesicles filled with virions. These virions are typical of *Coronavirus* in being clustered within membrane-bound vesicles derived from the endomembrane system, and in the electron-dense nucleocapsids appearing in section as dots within the virions (insets; circled enlargement of a virion with arrows pointing to nucleocapsid cross-sections). The virions are generally spherical, with a maximum measured diameter of 127 nm. The dotted line demarcates the trophoblast from the stroma; N = nucleus; scale bars (insets) = 0.1 μm .