Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 489–490

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

SARS-CoV-2 ACE-receptor detection in the placenta throughout pregnancy

Carole Gengler [1], Estelle Dubruc [1], Guillaume Favre [2], Gilbert Greub [3], Laurence de Leval [1], David Baud [2,*]

[1)] Institute of Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2)] Materno-fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[3)] Center for Research on Intracellular Bacteria, Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, CH-1011, Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 5 August 2020
Received in revised form
14 September 2020
Accepted 25 September 2020
Available online 3 October 2020

Editor: S. J. Cutler

Fetal risks for women exposed to SARS-CoV-2 and subsequent pregnancy outcomes remain uncertain [1]. Recent reports have raised controversial concerns regarding the potential for vertical transmission by transplacental infection. It has been proposed that the occurrence of intrauterine transplacental SARS-CoV-2 among infected mother–infant dyads be based upon identification of SARS-CoV-2 in chorionic villous cells using immunohistochemistry or nucleic acid methods such as in situ hybridization [2]. Hypothetically, two conditions are necessary for transplacental transmission to be possible: (a) the virus must reach the placenta; and (b) the receptor for the virus, angiotensin-converting enzyme 2 (ACE2), must be present in the placenta.

Regarding the first condition, we and others recently reported RT-PCR or RNAscope data supporting the presence of SARS-CoV-2 in placental tissue [3–6]. To date, conflicting data exists regarding the second condition [4,7,8].

In order to investigate ACE2 expression in the placenta throughout pregnancy, we selected formalin-fixed placental tissues between 14 and 40 weeks gestation from 28 patients who delivered before the current COVID-19 outbreak (two different cases for each 2 weeks of gestation, i.e. 14, 16, 18, … 38, 40 weeks; please see supplementary material), as well as placental tissues at 19 weeks' gestation from a COVID-19-positive patient (Fig. 1). Kidney was used as positive (brush border of proximal renal tubules and podocytes of glomeruli) and negative (distal renal tubules and renal medulla) controls. Using a monoclonal anti-ACE2 antibody (Atlas antibodies, clone CL4035, dilution 1/1000), we demonstrated in situ expression of ACE2 at the maternal–fetal interface (Fig. 1 and supplementary material), a prerequisite for transplacental transmission. We observed a strong and diffuse membranous staining of cytotrophoblast and syncytiotrophoblast cells of placental villi, as well as a membranous expression in extravillous trophoblast. By testing placental tissues at various gestational ages in both COVID-19-positive and -negative mothers, we confirmed that ACE expression is present consistently throughout pregnancy regardless of COVID-19 status.

Our in situ analyses by specific immunohistochemistry and SARS-CoV-2 detection by RT-PCR indicate a possible placental infection by SARS-CoV2. Trophoblastic cells, which are in direct contact with the maternal blood in the intervillous space, show strong expression of ACE2 throughout pregnancy, supporting that SARS-CoV2 is able to infect the placenta via a receptor-mediated mechanism. SARS-CoV-2 can cross the placental barrier, as it has been demonstrated in a neonate born to a mother infected in the last trimester and presenting with neurological compromise [5]. However, the rate of vertical transmission to the fetus warrants further investigation. By analogy to other pathogens (i.e. cytomegalovirus or toxoplasmosis), this may occur once sufficient time has elapsed for the virus to breach the placental barrier (6–8 weeks after infection).

SARS-CoV-2 infection of the maternal placental surface may induce acute or chronic placental insufficiency [3–5] or be responsible for subsequent miscarriage or fetal growth restriction as reported in 40% of MERS or SARS-1 maternal infections. In consequence, these findings could lead to increased protective measures for pregnant women, as well as a heightened level of concern/monitoring of pregnancies exposed to SARS-CoV-2.

* Corresponding author: D. Baud, Materno-fetal & Obstetrics Research Unit, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Vaudois (CHUV), 1011, Lausanne, Switzerland. Tel.: +41 79 556 13 51.
E-mail address: david.baud@chuv.ch (D. Baud).

https://doi.org/10.1016/j.cmi.2020.09.049

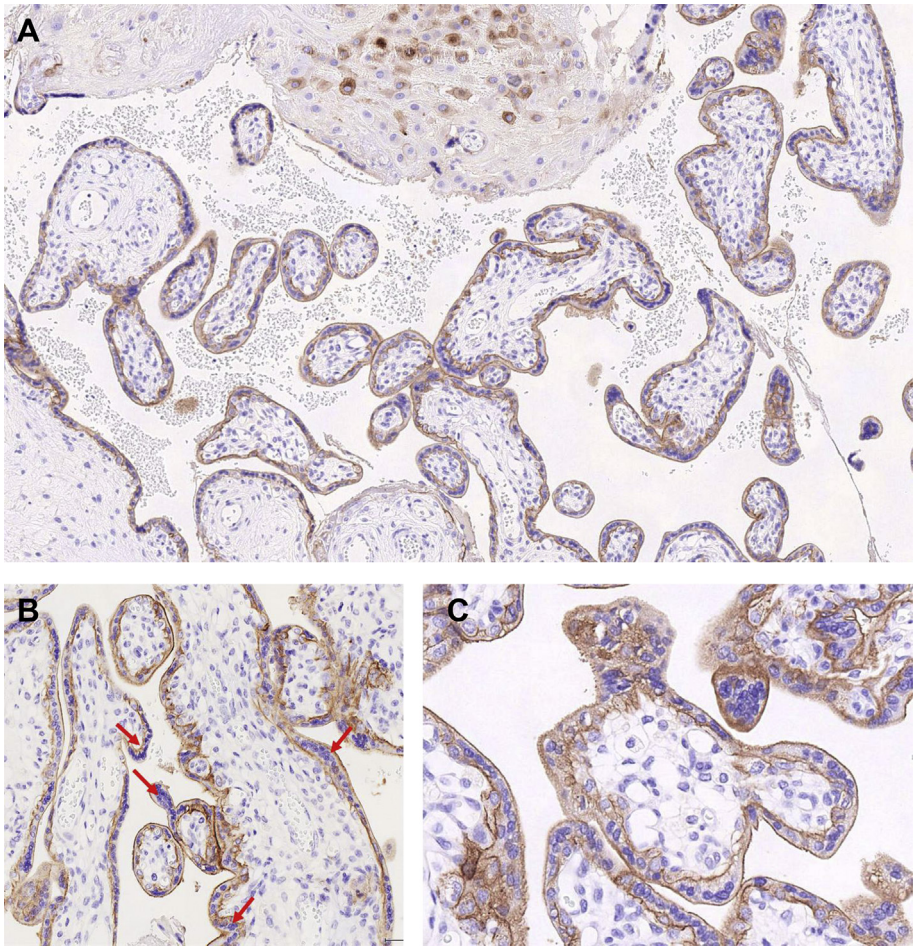

Fig. 1. Diffuse membranous staining of villous cytotrophoblast and syncytiotrophoblast cells (arrows) with monoclonal Anti-ACE2 antibody (clone CL4035), dilution 1/1000 in a COVID-19 positive mother, 19 weeks of amenorrhea.

Transparency declaration

G.G. reported having ongoing research agreements with Resistell and Becton-Dickinson and being medical advisor for Resistell; he also reported being developer of a card game on microbes and funding JeuPro, a start-up company that distributes the game Krobs. No other disclosures were reported by any of the other authors. No external funding was received.

Author contributions

D.B. and C.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: C.G., E.D., D.B.

Acquisition, analysis, or interpretation of data: all authors. Writing – original draft: C.G., E.D., D.B. Writing – review and editing: C.G., G.G., G.F., L.L., D.B. Administrative, technical, or material support: all authors. Supervision and validation: C.G., D.B.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.09.049.

References

[1] Bahadur G, Homburg R, Yoong W, Singh C, Bhat M, Kotabagi P, et al. Adverse outcomes in SAR-CoV-2 (COVID-19) and SARS virus related pregnancies with probable vertical transmission. JBRA Assist Reprod 2020;24:351–7.
[2] Schwartz DA, Morotti D, Beigi B, Moshfegh F, Zafaranloo N, Patane L. Confirming vertical fetal infection with COVID-19: neonatal and pathology criteria for early onset and transplacental transmission of SARS-CoV-2 from infected pregnant mothers. Arch Pathol Lab Med 2020. https://doi.org/10.5858/arpa.2020-0442-SA.
[3] Baud D, Nielsen-Saines K, Qi X, Musso D, Pomar L, Favre G. Authors' reply. Lancet Infect Dis 2020;20:775–6.
[4] Kotlyar A, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2020.
[5] Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11:3572.
[6] Patane L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM 2020;2:100145.
[7] Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal–fetal interface and fetal organs by single-cell transcriptome study. PloS One 2020;15:e0230295.
[8] Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Alazizi A, et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? Elife 2020;9.