EBioMedicine 60 (2020) 102983

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Characterizing COVID-19 maternal-fetal transmission and placental infection using comprehensive molecular pathology

David A. Schwartz[a,*], Kristen M. Thomas[b]

[a] Department of Pathology, Medical College of Georgia, Augusta, GA, United States
[b] Department of Pathology, NYU Langone Health – Main Campus & Bellevue Hospital Center, New York University School of Medicine, New York, NY, United States

ARTICLE INFO

Article History:
Received 11 August 2020
Accepted 17 August 2020
Available online xxx

Among the most worrisome consequences of a newly emergent viral disease is its potential effect on pregnant women. It is particularly important to determine whether a novel virus is transmissible from a mother to her infant, a process termed vertical infection, and if so, under what circumstances. There are three possible mechanisms for vertical infection – intrauterine infection (including transplacental and ascending infections), intrapartum transmission (during delivery), and postpartum infection. Intrauterine transplacental transmission is an important cause of vertical infection of the foetus from viruses, having occurred in previous epidemics of emergent viral diseases such as HIV, Ebola, hepatitis E and Zika viruses. However, following the birth of a neonate that is subsequently found to have a viral infection, it can be challenging to determine exactly how and when the infant became infected. These details have important implications that can influence obstetrical management decisions, best practice delivery options, and neonatal care including viral testing strategies, skin-to-skin maternal contact, need for neonatal isolation and safety of breast feeding.

In previous epidemics of such pathogenic coronaviruses as SARS and MERS, as well as other RNA respiratory viruses, transplacental infections have either been absent or were rare [1]. However, increasing reports of neonates testing positive for COVID-19 shortly after birth have focused attention on the possibility of intrauterine infection, and specifically on transplacental transmission [2]. Until recently, it has not been possible to determine how newborn infants acquired their infection, leading investigators to speculate on when, how and from whom they acquired COVID-19 [3].

Examination of the placenta is a potentially valuable method for the determination of intrauterine transplacental transmission of a virus from an infected mother to her foetus [3]. In prior epidemics of emerging viral infections including Ebola [4] and Zika viruses [5], molecular pathology techniques have proven important in demonstrating virus in infected foetal cells of the placenta and confirming transplacental maternal-foetal transmission. These methods include immunohistochemistry using antibodies to viral antigens and nucleic acid techniques such as in situ hybridization and RNAscope that detect target RNA molecules within intact cells. Both antibody-based and nucleic acid methodologies can precisely identify virus within specific cell types in defined anatomic compartments of the placenta and they are not limited by standard formalin fixation. Molecular pathologic analysis of the placenta may also be used to identify and immunophenotype inflammatory cells of both maternal and foetal origins, characterizing the nature of the immunological response to placental infection. Double-staining methods can evaluate individual cells in the placenta for two different markers, permitting simultaneous identification of the virus and cell types. Additionally, immunohistochemistry can identify specific proteins, cytoskeletal components and markers of cell activation which can help determine responses at the maternal-foetal interface to viral infection.

In this issue of *EBioMedicine*, Facchetti and colleagues [6] describe their research involving the placenta from a term neonate who tested positive for COVID-19 and developed pneumonia and systemic disease following delivery to an infected mother. A comprehensive pathological evaluation of the placenta was performed to identify SARS-CoV-2 in foetal tissue, characterize the nature of the pathologic response to the infection, identify and immunophenotype the cells and characterize the inflammatory response. Using routine staining methods, the placenta showed foetal vascular malperfusion and a prominent inflammatory infiltrate in the intervillous space. An extensive array of antibody tests to determine the immunophenotype of the inflammatory cells revealed a heterogenous mixture of monocyte-macrophages and mature and immature neutrophils. Despite the prominent number of neutrophils, immunofluorescence antibody staining demonstrated limited positivity for neutrophil extracellular traps (NETS). Villous stromal macrophages, termed Hofbauer cells,

E-mail address: davidalanschwartz@gmail.com (D.A. Schwartz).

https://doi.org/10.1016/j.ebiom.2020.102983

were increased in number and expressed programmed death-ligand 1 (PD-L1). Immunohistochemical staining for antibodies recognizing megakaryocyte and platelet associated antigens showed significant platelet deposition in areas of inflammation. Damage to the syncytiotrophoblast was confirmed using cytokeratin antibody staining.

Perhaps the most significant finding by the authors was the demonstration of intense signal positivity for SARS-CoV-2 in syncytiotrophoblast lining the chorionic villi using RNA in situ hybridization. The syncytiotrophoblast is a major component of the maternal-foetal interface and constitutes its strongest cellular defensive mechanism together with the innate immune mechanism [7]. The finding of SARS-CoV-2 nucleic acid in this continuous cell layer demonstrates infection of foetal tissue and identifies a pathway for the intrauterine infection of the foetus. In addition to the evidence from nucleic acid analysis, ultrastructural examination revealed coronavirus-like particles within the cytoplasm of syncytiotrophoblast, as well as within chorionic villous fibroblasts and foetal capillary endothelial cells.

In a recent communication Schwartz and colleagues [3] proposed that the diagnosis of intrauterine transplacental SARS-CoV-2 among infected mother-neonate dyads be based upon identification of SARS-CoV-2 in foetal-derived cells of the chorionic villi using immunohistochemistry or nucleic acid methods such as in situ hybridization. In their article, Facchetti and coauthors have satisfied these criteria and demonstrated that SARS-CoV-2 can enter the placenta and be passed to the foetus prior to delivery. This finding not only confirms the recent results of placental infection in other neonates with COVID-19 [8, 9] but introduces new questions. How do these findings correlate with recent research examining the presence of receptors (ACE2) and enzymes (TMPRSS2) in placental tissues that are necessary for viral entry and replication [10]? Do Hofbauer cells have a role in either preventing or permitting transmission? Are there any risk factors for transplacental transmission of the virus in mothers with COVID-19? Is maternal or foetal vascular malperfusion of the placenta causally associated with the infection or coincidental? As the COVID-19 pandemic continues to spread, hopefully these and related questions will be answered.

Author contributions

The authors contributed equally.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] Schwartz DA, Dhaliwal A. Infections in pregnancy with COVID-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: experiences with coronaviruses, HPIV, hMPV RSV, and influenza. Arch Pathol Lab Med. 2020. doi: 10.5858/arpa.2020-0211-SA.

[2] Schwartz DA, Mohagheghi P, Beigi B, Zafaranloo N, Moshfegh F, Yazdani A. Spectrum of neonatal COVID-19 in Iran: 19 infants with SARS-CoV-2 perinatal infections with varying test results, clinical findings and outcomes. J Matern Fetal Neonatal Med. 2020. https://doi.org/10.1080/14767058.2020.1797672.

[3] Schwartz DA, Morotti D, Beigi B, Moshfegh F, Zafaranloo N, Patanè 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.

[4] Muehlenbachs A, de la Rosa Vazquez O, Bausch DG, Schafer IJ, Paddock CD, Nyakio JP, et al. Ebola virus disease in pregnancy: clinical, histopathologic, and immunohistochemical findings. J Infect Dis 2017;215(1):64–9. https://doi.org/10.1093/infdis/jiw206.

[5] Schwartz DA. Viral infection, proliferation, and hyperplasia of Hofbauer cells and absence of inflammation characterize the placental pathology of fetuses with congenital Zika virus infection. Arch Gynecol Obstet 2017;295(6):1361–8. doi: 10.1007/s00404-017-4361-5.

[6] Facchetti F, Bugatti M, Drera E, Tripodo C, Sartori E, Cancila V, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. EBioMed 2020.

[7] Ander SE, Diamond MS, Coyne CB. Immune responses at the maternal-fetal interface. Sci Immunol 2019;4(31) eaat6114. doi: 10.1126/sciimmunol.aat6114.

[8] Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of COVID-19: sARS-CoV-2 RNA on the fetal side of the placenta in pregnancies with COVID-19 positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020:100145. doi: 10.1016/j.ajogmf.2020.100145.

[9] 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. https://doi.org/10.1038/s41467-020-17436-6.

[10] 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:e58716. doi: 10.7554/eLife.58716.