International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 4 Issue 5, July-August 2020 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

COVID-19: Transplacental SARS-CoV-2 Transmission

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KEYWORDS: *SARS-CoV-2, COVID-19, pregnancy, SARS-CoV, MERS-CoV, preventive measures*

How to cite this paper: Takuma Hayashi | Ikuo Konishi "COVID-19: Transplacental SARS-CoV-2 Transmission" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-4 | Issue-5, August 2020, pp.1466-1468, URL: www.ijtsrd.com/papers/ijtsrd33191.pdf

IJTSRD33191

Abstract

"Mother-to-child transmission" is the transmission of microorganisms (bacteria, viruses, etc.) from mothers to babies. There are three types of mother-to-child infections: "infant infection" in which the baby is infected in the abdomen, "birth canal infection" which is transmitted when the baby begins to pass through the birth canal, and "breast milk infection". In most cases, certain infections during pregnancy can make the mother more severe, and the infection can affect the baby in the abdomen. Angiotensin converting enzyme II (ACE2), which is a host-side receptor for Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2), is expressed in placental cells. Currently, the new coronavirus infection disease-2019(COVID-19) has been a problem for an adverse effect on pregnancy. Most pregnant women hospitalized with SARS-CoV-2 have mid-to late trimesters with favorable, not severe, outcomes. Previous clinical reports have revealed that mother-to-child transmission is rare. However, recently, a case was reported in which SARS-CoV-2 was transmitted to the fetus through the placenta. In this Short Comment, we would like to discuss new information about mother-to-child transmission of SARS-CoV-2, including new information.

In the early cases of the new coronavirus infection disease-2019(COVID-19), an association between the fresh market for buying and selling live animals and Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) infected persons was found in Wuhan, China(1).It has been pointed out that SARS-CoV-2 may initially have transmitted from animals to humans. Mainly, SARS-CoV-2 infects humans through the airborne droplets scattered by the cough and sneeze of the infected person(2).Based on the results of clinical studies to date, COVID-19 infection spreads to individuals infected before COVID-19 symptoms and individuals who do not develop COVID-19(3).Many SARS-CoV-2 infected individuals have no or mild symptoms. However, some people infected with SARS-CoV-2 become more severe and die. In many of the SARS-CoV-2-infected persons, symptoms of COVID-19 is observed to about 2 to 14 days after infection. The risk of seriousness and mortality in SARS-CoV-2 infected individuals increases with age. Moreover, the risk of seriousness and death is even higher in people with underlying diseases such as heart, lung, kidney, liver disease, diabetes, obesity, immunodeficiency.

Human angiotensin converting enzyme II (ACE2) receptor has been reported as a host-side receptor to which SARS-CoV-2, which is the causative virus of COVID-19, binds when entering human cells(4)(Figure 1). On February 25, 2020, Renhong Yan *et al.*, West Lake University, China, revealed the full-length conformation of ACE2 receptor required for new coronavirus (SARS-CoV-2) to infect human cells(5). In addition, a cryo-electron micrograph showing the binding state between the receptor binding domain (RBD) on the viral spike (S) glycoprotein and the interaction region of the ACE2 receptor was reported.

The ACE2 receptor is expressed in mucosal epithelial cells of the upper respiratory tract (nasal cavity, pharynx, larynx), heart, lung, small intestine, kidney, testis, placenta, and the like(6) (Figure 2).First, SARS-CoV-2 infects mucosal epithelial cells of the upper respiratory tract (nasal cavity, pharynx, larynx).SARS-CoV-2 invades mucosal epithelial cells, proliferates, and germinates the virus extracellularly. New infected cells are generated in the course of the viral life cycle. In particular, SARS-CoV-2 adsorption, proliferation and release occurs in the upper respiratory tract. It was reported that SARS-CoV-2 carried by a mother who was positive by virus test could be transmitted to the fetus through the placenta(7).Previous studies have suggested that transmission of SARS-CoV-2 may occur during the perinatal period (before and after childbirth)(8). However, it is unclear whether SARS-CoV-2 transmission occurs through the placenta, via the transcervical route, or as a result of exposure to environmental factors.

Now, the team of Daniele De Luca et al. presents the results of a study showing possible transplacental transmission of SARS-CoV-2(7). In this case, a pregnant woman in her 20s was hospitalized with fever and a severe cough, SARS-CoV-2 E gene (envelope protein) and S gene (encoding spike protein) were confirmed by the blood test, nasopharyngeal

swab test and vaginal swab test of the pregnant woman. Newborn nasopharyngeal and anal swab tests were performed 1 hour, 3 days and 18 days after the delivery of the newborn by Caesarean section(7).A positive reaction against E and S genes of SARS-CoV-2 was detected by these inspections. Further, by the blood test and bronchoalveolar lavage fluid examination of newborn, SARS-CoV-2 positive reactivity was confirmed(7).According to the observations of De Luca et al., the infant had neurological symptoms associated with SARS-CoV-2 infection similar to those reported for adult patients(7). Neuroimaging showed signs of white matter injury. De Luca et al. speculate that these symptoms were caused by vascular inflammation induced by SARS-CoV-2 infection(7).No viral or bacterial infection other than SARS-CoV-2 was detected in this infant. All other neonatal diseases that could cause these clinical symptoms was never observed. Both the mother and the infant recovered from SARS-CoV-2 infection and were discharged(7).

Dr. De Luca and colleagues reveal measurements that placental virus levels were higher than those in amniotic fluid and maternal blood (7). This result suggests that SARS-CoV-2 is actively replicating in placental cells and may cause neonatal viremia. These clinical findings were consistent with the level of inflammation found by histological examination of the placenta. From the positive result of SARS-CoV-2 in the placenta tissue and blood of the mother, and the blood of the newborn, maternal-to-fetal transmission of SARS-CoV-2 is likely to have occurred through the placenta(7).Further studies are needed to ascertain the maternal-to-fetal transmission route of SARS-CoV-2.

The development competition for vaccines and therapeutic agents against the new coronavirus is intensifying all over the world (11).The development of antibody drugs using "antibodies" that protect the body from foreign substances is under way. Antibody drugs are expected to be effective as therapeutic agents in addition to the possibility of being developed earlier than vaccines. As a result, development of various approaches to antibody drugs has been accelerated. Vaccination is too late for people already infected with the new coronavirus. However, administrations of antibodies are still potentially useful in the treatment of COVID-19 (12).In addition, IgG translocate through the placenta to the fetus. In general, vaccines are less effective against infants, the elderly, and people with immune disorders. For these people, treatment with antibody drugs is a long-awaited defense.

Data Sharing

Data are available on various websites and have been made publicly available (more information can be found in the first paragraph of the Results section).

Disclosure

The authors declare no potential conflicts of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank Professor Richard A. Young (Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA) for his research assistance. This study was supported in part by grants from the Japan Ministry of Education, Culture, Science and Technology (No. 24592510, No. 15K1079, and No. 19K09840), the Foundation of Osaka Cancer Research, The Ichiro Kanehara Foundation for the Promotion of Medical Science and Medical Care, the Foundation for Promotion of Cancer Research, the Kanzawa Medical Research Foundation, The Shinshu Medical Foundation, and the Takeda Foundation for Medical Science.

Author Contributions

T.H. performed most of the experiments and coordinated the project; T.H. conceived the study and wrote the manuscript. T.H. and I.K. gave information on clinical medicine and oversaw the entire study.

Transparency Document

The transparency document associated with this article can be found in the online version at http://

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Hayashi *et al*. Figure 1

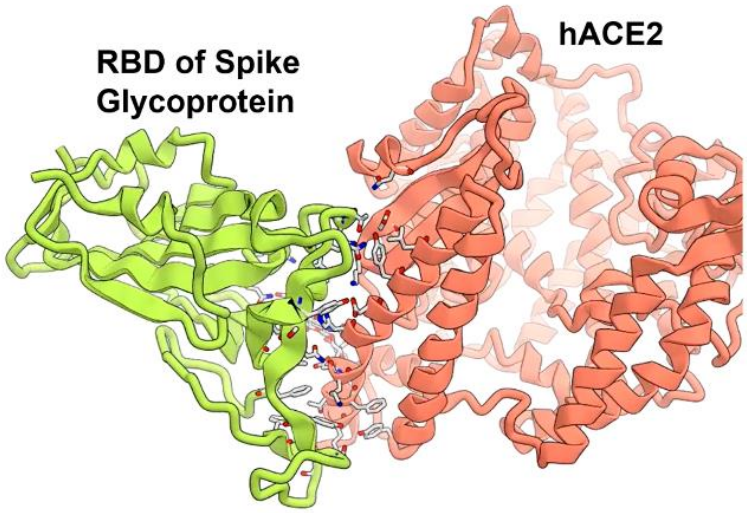

Figure 1. The pink protein is the interaction region of human ACE2 (hACE2).The green protein is the receptor binding domain (RBD) (ID PDB: 6VW1) of the spike glycoprotein of SARS-CoV-2. In this figure, the binding of human ACE2 (hACE2) to spike glycoprotein is shown. Overall structure of the SARS-CoV-2 RBD bound to hACE2. hACE2 is shown in green (8). The SARS-CoV-2 RBD core is shown in cyan and receptor-binding motif (RBM) in red. Disulfide bonds in the SARS-CoV-2 RBD are shown as sticks and indicated by arrows. The N-terminal helix of hACE2 responsible for binding is labelled.

Hayashi *et al*. Figure 2

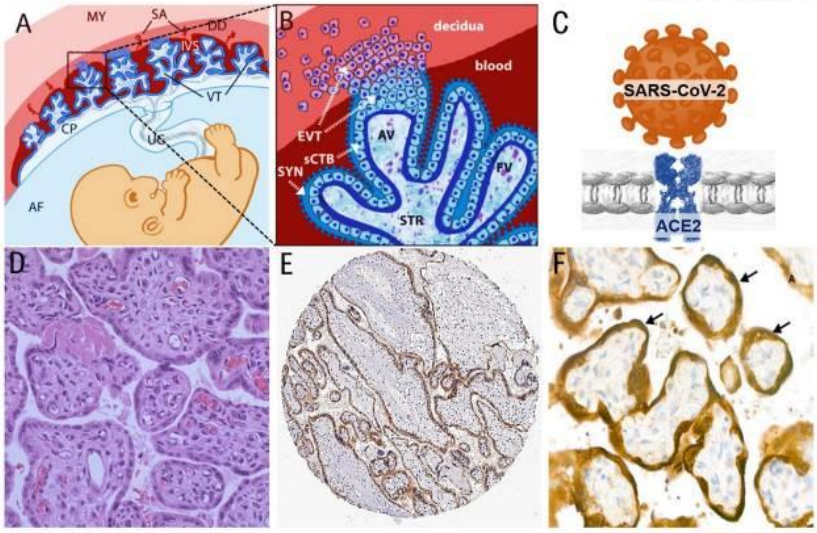

Figure 2. A. Early placental development cartoon showing trophoblast contribution to placental villi. The cytotrophoblast cells are the initial unfused trophoblast cells that cover the implanting blastocyst surface. **B.** In the late pregnancy placenta this cellular layer becomes squamous and discontinuous, with syncytiotrophoblast cells forming the main cellular barrier (9). Hyperglycosylated human Chorionic Gonadotropin (hCG) promotes the growth of cytotrophoblast cells and the endometrial invasion by these cells during implantation. SYN; syncytiotrophoblasts, sCTB; subsyncytial cytotrophoblasts (this layer grows increasingly discontinuous in later trimesters), EVT; extravillous cytotrophoblasts (anchor the villous tree in the decidua).**C.** Human ACE2 is a functional receptor that acts as an entry point into human lung cells for coronaviruses and plays a key role in both cross-species and human-to-human transmissions of the virus. A better understanding of the SARS-CoV-2-ACE2 interactions can lead to the development of anti-infective strategies such as human ACE2 protein blockade or the development of neutralizing antibodies. **D.** Placental H.&E. staining. As the placenta matures and increases in size in the second trimester, the villi become smaller and more vascular. The syncytiotrophoblast cell layer draws up into"syncytial knots"which are small clusters of cells, leaving a single cytotrophoblast layer. Clumps of pink fibrinbegin to appear between the chorionic villi. **E.** Human ACE2 strongly expresses on the surface of trophoblast cells in the placenta. **F.** Placental immunostaining for SARS-CoV-2 N-protein (anti-N immunohistochemistry, original magnification ×800). The intense brown cytoplasmic positivity of perivillous trophoblastic cells in the placenta of our case (arrows). The pathological result is adapted from Ref.10.