Intrauterine vertical transmission of SARS-CoV-2: what we know so far

Chen Wang[1], Yi-Hua Zhou[2]*, Hui-Xia Yang[1]*, Liona C. Poon[3]

[1]Department of Obstetrics and Gynaecology of Peking University First Hospital, Beijing, China;

[2]Department of Laboratory Medicine and Infectious Diseases, Nanjing Drum Tower Hospital, China;

[3]Department of Obstetrics and Gynaecology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR

* Joint corresponding authors

Correspondence to:

Hui-Xia Yang: Department of Obstetrics and Gynaecology, Peking University First Hospital, Beijing 100034, China (e-mail: yanghuixia@bjmu.edu.cn)

Yi-Hua Zhou: Department of Laboratory Medicine and Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing 210008, China (e-mail: zgr03summer@126.com)

Short title: Vertical transmission of SARS-CoV-2

Keywords: COVID-19, SARS-CoV-2, vertical transmission, intrauterine infection, congenital infection

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.22045

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been rapidly spreading worldwide and is now a global pandemic. One of the major concerns is whether SARS-CoV-2 can be vertically transmitted to fetuses, thus causing congenital infection.

The most convincing evidence of intrauterine transmission of COVID-19 would be to confirm the replication of SARS-CoV-2 in fetal pulmonary tissues, which is technically almost infeasible. Practically, the approach to investigating whether there has been intrauterine viral infection is to confirm the presence of the virus in placenta, amniotic fluid, cord blood and neonatal pharyngeal swab samples. It is important to emphasize that all of these samples need to be collected immediately after delivery and using aseptic technique, thus guaranteeing that the samples are not contaminated and best represent intrauterine conditions. The first study investigating the possibility of intrauterine transmission of COVID-19 infection was through testing SARS-CoV-2 in matched amniotic fluid, cord blood and neonatal pharyngeal swab samples using quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) in six pregnant women with mild to moderate manifestation and laboratory-confirmed COVID-19 infection and the results of all samples were negative suggesting that no intrauterine fetal infection occurred during the third trimester of pregnancy.[1] Subsequently, one study of four pregnancies that utilized similar methodologies demonstrated no evidence of vertical transmission in pregnant women with COVID-19 in the third trimester.[2] Furthermore, this

study also demonstrated that vaginal secretion samples also tested negative for SARS-CoV-2 RNA.[2] In a study by Chen et al.,[3] paired neonatal pharyngeal swab samples and placental tissues of three pregnant women with COVID-19 were used as samples to evaluate the potential risk of intrauterine vertical transmission, and all samples tested negative for SARS-CoV-2 RNA. Notably, a neonate born to a pregnant woman with COVID-19 tested positive for SARS-CoV-2 RNA in the pharyngeal swab sample at 36 hours after birth was subsequently confirmed that the qRT-PCR testing of the placenta and cord blood was negative for SARS-CoV-2, suggesting that intrauterine vertical transmission might not have occurred.[4,5] Thus, based on these existing data, there is currently no evidence for intrauterine infection caused by vertical transmission in women with COVID-19.

However, some questions remain unanswered. Most of the cases in the studies as described above had mild to moderate symptoms, and all manifested during the third trimester of pregnancy, and therefore the time interval from clinical manifestation of COVID-19 infection to delivery was short. Since the placental barrier may temporarily delay the transfer of the virus from the mother to the fetus, as observed in cytomegalovirus infection, it is uncertain whether there could be a risk of vertical transmission when the COVID-19 infection occurs in the first or second trimester, or when there is a long clinical manifestation-to-delivery interval. Additionally, there appear some ways through which SARS-CoV-2 can potentially cause intrauterine infection by transplacental vertical transmission. A study by Zhao et al. has

demonstrated that angiotensin-converting enzyme 2 (ACE2), which has recently been indicated as the surface receptor of sensitive cells for SARS-CoV-2,[6] is expressed in human placentas.[7] This opens up the possibility for SARS-CoV-2 to spread transplacentally through ACE2. On the other hand, placental barrier damage caused by severe maternal hypoxemia in women with COVID-19 infection could also be one potential way through which SARS-CoV-2 can cause intrauterine infection by vertical transmission.

Most recently, two studies have explored the possibility of vertical transmission of SARS-CoV-2 in a combined total of seven affected pregnancies from the perspective of testing for SARS-CoV-2 specific antibodies (IgG and IgM) in neonatal serum samples.[8,9] The conclusion was that SARS-CoV-2 could be transmitted in utero based on the presence of IgM antibodies, detected by the recently developed automated chemiluminescence immunoassays, in blood drawn from three neonates following birth. However, all of the three neonatal respiratory samples tested negative for SARS-CoV-2 RNA, and there was no direct evidence provided by testing cord blood or placenta. Of note, the sensitivity and specificity of the assays used in the two studies have not been extensively evaluated.[10] Furthermore, as is known to all, IgM assays are easily prone to false-positive results.[10]

When using specific IgG and IgM antibodies as a method to detect viral infection, it is important to observe for the kinetic changes of the IgM and IgG antibodies. The study by Zeng et al. did not evaluate the dynamic changes of SARS-CoV-2 IgM/IgG in the neonates.[8] Whereas,

in the study by Dong et al., the observed decline of SARS-CoV-2 IgG from 140.32 AU/mL (normal range 0-10 AU/ml) at 2 hours of life to 69.94 AU/mL on day 14 of life and of IgM from 45.83 AU/mL (normal range 0-10 AU/ml) at 2 hours of life to 11.75 AU/mL on day 14 of life is not consistent with the typical profile of the body's antibody response to acute viral infection.[9] As the half-life of IgG antibodies is around 21-23 days, and the time lag between the development of SARS-CoV-2 IgG and IgM antibodies is about one week,[11-12] the rapid decline ([140.32-69.94]/140.32=50%) of SARS-CoV-2 IgG in the infant within 14 days, while there had been a decline in IgM antibodies, strongly indicates that the neonatal SARS-CoV-2 IgG was transplacentally derived from the mother, and was not actively induced by the presumed neonatal infection. In our opinion, these two studies have not provided concrete evidence to prove that SARS-CoV-2 infection can be acquired in utero.

Furthermore, in a cohort study by Zeng et al.,[13] 3 of 33 (9%) infants were diagnosed with neonatal early-onset infection with SARS-CoV-2 based on positive qRT-PCR results of the nasopharyngeal and anal swabs in two consecutive tests at day 2 and 4 of age. Though, strict infection control and prevention measures were implemented during the delivery, one cannot completely exclude postpartum infections because of the delay in testing. All three infants tested negative for SARS-CoV-2 RNA by day 6/7.[13] Whether the neonatal infection can cause the same virologic profiles as adult infection requires further investigation.

High quality research is required to clarify whether SARS-CoV-2 can be transmitted from the mother to the fetus in utero transplacentally. First, we propose that cohort studies in evaluating the risk of fetal adverse outcomes, including structural malformation, miscarriage and fetal growth restriction, in pregnant women with COVID-19 contracted during the first and second trimester would be essential in investigating whether there is vertical transmission of SARS-CoV-2. Second, appropriately matched biological samples collected immediately after delivery, using aseptic technique, from women with COVID-19 are important to help indicate whether SARS-CoV-2 can be transmitted vertically. These biological samples include cord blood, placental tissue, amniotic fluid and amnion-chorion interface swab. Though we do not assume the fetus to acquire the virus through the respiratory route, we believe that the neonatal pharyngeal swab should also be one of the suitable biological samples for the detection of SARS-CoV-2 RNA as the virus is detectable in the upper airway because it is propagated proximally by epithelial cilia of the respiratory tract. If possible, testing of miscarried fetus and placenta of COVID-19-infected pregnant women for SARS-CoV-2 should be undertaken. Third, in addition to testing for SARS-CoV-2 RNA by qRT-PCR, serological test could be an important supplement in order to clarify the issue of vertical transmission of SARS-CoV-2. However, longitudinal follow-up for infants of women with COVID-19 during pregnancy is required. For example, when the biological samples that have been collected immediately after birth are negative for SARS-CoV-2 RNA, but the IgM and IgG antibodies are positive in the newborn, longitudinal follow-up of the IgG antibody concentrations in the infant is required. If the IgG

antibodies in the infant become negative within six months, the possibility of intrauterine infection can be ruled out, and if the IgG antibodies in the infant persist till the age of eighteen months or beyond, the diagnosis of congenital infection can be confirmed after exclusion of infection during infancy.

Declaration of interests

The authors declare that there are no conflicts of interest in this manuscript.

References

1. Chen H, Guo J, Wang C, Fan Luo, Xuechen Yu, Wei Zhang, Jiafu Li, Dongchi Zhao, Dan Xu, Qing Gong, Jing Liao, Huixia Yang, Wei Hou, Yuanzhen Zhang. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395:809-15. DOI: 10.1016/S0140-6736(20)30360-3.

2. Lei D, Wang C, Li C, Fang C, Yang W, Cheng B, Wei M, Xu X, Yang H, Wang S, Fan C. Clinical characteristics of COVID-19 in pregnancy: analysis of nine cases. Chin J Perinat Med. 2020, 23 (03) : 225-231. DOI:10.3760/cma.j.cn113903-20200216-00117.

3. Chen S, Huang B, Luo D, Li X, Yang F, Zhao Y, Nie X, Huang B. Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. Chinese Journal of Pathology. 2020,49(00):E005-E005. DOI:10.3760/cma.j.cn112151-20200225-00138 .

4. Yu N, Li W, Kang Q, Zhi Xiong, Shaoshuai Wang, Xingguang Lin, Yanyan Liu, Juan Xiao, Haiyi Liu, Dongrui Deng, Suhua Chen, Wanjiang Zeng, Ling Feng, Jianli Wu. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020.Online ahead of print. DOI:10.1016/S1473-3099(20)30176-6

5. Wang S, Guo L, Chen L, Weiyong Liu, Yong Cao, Jingyi Zhang, Ling Feng. A case report of neonatal COVID-19 infection in China.Clin Infect Dis. 2020. pii: ciaa225. Online ahead of print.DOI: 10.1093/cid/ciaa225.

6. Yu Zhao, Zixian Zhao, Yujia Wang, Yueqing Zhou, Yu Ma, Wei Zuo. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv 2020. DOI: https://doi.org/10.1101/2020.01.26.919985.

7. G. Valdesa, L A A Neves, L Anton, J Corthorn, C Chacón, A M Germain, D C Merrill, C M Ferrario, R Sarao, J Penninger, K B Brosnihan. Distribution of Angiotensin-(1-7) and ACE2 in Human Placentas of Normal and Pathological Pregnancies.Placenta. 2006, 27, 200e207. DOI: 10.1016/j.placenta.2005.02.015.

8. Zeng H, Xu C, Fan J, Yueting Tang, Qiaoling Deng, Wei Zhang, Xinghua Long. Antibodies in infants born to mothers with COVID-19 pneumonia.JAMA. 2020. Online ahead of print.DOI: 10.1001/jama.2020.4861.

9. Dong L, Tian J, He S, Chuchao Zhu, Jian Wang, Chen Liu, Jing Yang. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020.Online ahead of print. DOI: 10.1001/jama.2020.4621.

10. David W. Kimberlin, Sergio Stagno. Can SARS-CoV-2 Infection Be Acquired In Utero? More Definitive Evidence Is Needed. JAMA. 2020. Online ahead of print.DOI: 10.1001/jama.2020.4868.

11. Li Guo, Lili Ren, Siyuan Yang, Meng Xiao, De Chang, Fan Yang, Charles S Dela Cruz, Yingying Wang, Chao Wu, Yan Xiao, Lulu Zhang, Lianlian Han , Shengyuan Dang , Yan Xu, Qiwen Yang, Shengyong Xu, Huadong Zhu, Yingchun Xu, Qi Jin , Lokesh Sharma, Linghang Wang, Jianwei Wang. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19).Clin Infect Dis 2020. Online ahead of print. DOI:10.1093/cid/ciaa310.

12. Juanjuan Zhao, Quan Yuan, Haiyan Wang, Wei Liu, Xuejiao Liao, Yingying Su, Xin Wang, Jing Yuan, Tingdong Li, Jinxiu Li, Shen Qian, Congming Hong, Fuxiang Wang, Yingxia Liu, Zhaoqin Wang, Qing He, Zhiyong Li, Bin He, Tianying Zhang, Yang Fu, Shengxiang Ge, Lei Liu, Jun Zhang, Ningshao Xia, Zheng Zhang.Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019.Clinical Infectious Diseases,2020. Online ahead of print. DOI: org/10.1093/cid/ciaa344.

13. Zeng L, Xia S, Yuan W, et al., Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China.JAMA Pediatr. 2020.Online ahead of print.DOI: 10.1001/jamapediatrics.2020.0878.