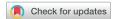


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Comment on evidence for and against vertical transmission of severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019)



TO THE EDITORS: We read with great interest Lamouroux's discussion of vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 They report a low frequency (1%) of serum SARS-CoV-2 ribonucleic acid (RNA) viral load (RNAemia) and a low expression of the angiotensinconverting enzyme 2 (ACE2) receptor in the maternal-fetal interface between 6 and 14 weeks' gestation as arguments against biologic plausibility of vertical transmission in the first trimester of pregnancy. We would like to expand the discussion regarding vertical transmission.

Vertical transmission of maternal pathogens may occur transplacentally via amniotic fluid infection or as an ascending infection. Presumably, for hematogenous or transplacental transmission, maternal viremia would be required. A study by Huang et al² showed a 15% frequency of RNAemia among adults with symptomatic coronavirus disease 2019.

Consistent with Lamouroux's statement that ACE2 is low in the first trimester of pregnancy, ACE2 RNA expression is developmentally regulated with extremely low expression at 6 to 14 weeks' gestation, although there is high expression at 24 weeks' gestation.³ ACE2 RNA is highly expressed in human villous trophoblast, extravillous trophoblast, and syncytiotrophoblast as well as in several fetal organ cells (such as the heart, liver, and lung but not the kidneys) at 24 weeks' gestation.³ Interestingly, another study demonstrated ACE2 protein expression in human syncytiotrophoblast by immunocytochemistry at 6 to 16 weeks' gestation and at term.⁴ In placental villi, the main sites of immunocytochemical expression of ACE2 are the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of primary and secondary villi. The presence of an ACE2 receptor in gestational tissue raises the possibility of vertical transmission.

In utero or congenital infection of SARS-CoV-2 via amniotic fluid has been suggested, with positive polymerase chain reaction (PCR) results in amniotic fluid obtained by needle aspiration after uterine incision but before amniotomy during a cesarean delivery at 32 weeks' gestation, with precautions taken to prevent environmental contamination of specimens.⁶ The PCR test for SARS-CoV-2 was negative in vaginal secretions, umbilical cord blood, and neonatal nasopharynx samples at birth but was positive in nasopharyngeal samples at 24 hours.⁶

Placental infection (PCR test that is positive for SARS-CoV-2 in placental submembrane and cotyledon samples) has also been demonstrated in a pregnancy with miscarriage in the second trimester.⁷ Placental histology demonstrated mixed inflammatory infiltrates composed of neutrophils and monocytes in the subchorial space and nonspecific increased intervillous fibrin deposition and funisitis in the absence of bacterial or fungal infection.

Whether in utero (hematogenous or transamniotic) infection or placental infection is possible is not clear yet, but it certainly appears plausible. We would advocate that translational, systematic evaluation demonstrating an infectious virus in paired maternal and infant tissue samples is required to better address this question of vertical transmission.

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The authors report no conflict of interest.

REFERENCES

- 1. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville V, Ville Y. Evidence for and against vertical transmission for SARS-CoV-2 (COVID-19). Am J Obstet Gynecol 2020;223:91.e1-4.
- 2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395: 497-506.
- 3. 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.
- 4. Pringle KG, Tadros MA, Callister RJ, Lumbers ER. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta 2011;32:956-62.
- 5. Valdés G, Neves LA, Anton L, et al. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathological pregnancies. Placenta 2006;27:200-7.
- 6. Zamaniyan M, Ebadi A, Aghajanpoor S, Rahmani Z, Haghshenas M, Azizi S. Preterm delivery, maternal death, and vertical transmission in a pregnant woman with critical COVID-19 infection. Prenat Diagn 2020. [Epub ahead of print].
- 7. Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA 2020;323:2198-200.
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