Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 06/22/2020
Approved on: 06/24/2020

REVIEW ARTICLE

Vertical transmission of COVID-19: an integrative review

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Keywords:
Infectious Disease Transmission
Vertical
Neonatology
Coronavirus Infections
Betacoronavirus.

Abstract

Introduction: The current pandemic of COVID-19 raises the need for knowledge about the impact of the new coronavirus on the health of humanity globally. To date, little evidence has been reported on the possibility of vertical transmission of the disease. **Objective:** To present scientific evidence, based on an integrative literature review, on the possibility of vertical transmission of COVID-19. **Methods:** The bibliographic survey was carried out through the MEDLINE bibliographic bases, in the U.S. National Library of Medicine and the National Institute Health (PubMed) interface; Latin American and Caribbean Literature on Health Sciences (LILACS) and Cochrane. The descriptors were selected using Medical Heading Terms (MeSH): "vertical transmission", "neonatology", "COVID-19", "SARS-CoV-2". The search was limited to articles in English, Spanish and Portuguese, with publication date of the last 10 years (2010 to 2020). 14 studies were selected from case report, literature review, editorial and case series. **Conclusion:** Some studies demonstrate the existence of vertical transmission of COVID-19, while others consider that the data presented do not support this statement. Therefore, further studies are needed for adequate proof.

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INTRODUCTION

At the end of 2019, a new coronavirus, named by the World Health Organization (WHO), as COVID-19/SARS-CoV-2[1] was identified in the Wuhan province, China. SARS-CoV-2 is part of a large family of RNA viruses, which causes diseases ranging from a common cold to more serious and potentially fatal conditions, with intense lung involvement[2].

Mainly droplets transmit SARS-CoV-2 infection; however, knowing the viral pathophysiology, it is important to investigate other forms of transmission, especially transplacental[3]. Coronavirus infects human cells by binding proteins from viral spikes to cellular receptors, such as angiotensin-converting enzyme 2 (ACE2) molecules and transmembrane serine protease 2 (TMPRSS2), both with protease activity and widely expressed in various tissues and human organs, including the uterus and the placenta[4,5,6].

Chen et al. (2020), investigated the presence of SARS-CoV-2 in samples obtained from amniotic fluid, umbilical cord blood, smear from the neonatal throat and breast milk, using RT-PCR, from six patients in order to analyze the potential for vertical transmission of COVID-19. The authors found no evidence of vertical transmission in late pregnancy[7]. Zhu et al. (2020), who found no evidence of congenital transmission of SARS-CoV-2[8], have showed similar data.

On the other hand, Zeng et al. (2020) showed the presence of IgM and IgG in the serum of children born to mothers with COVID-19 pneumonia[9]. However, Procianoy et al. (2020) consider that these findings are not sufficient to confirm the congenital transmission of the infection[10].

In view of these findings, we decided to carry out an integrative literature review on the evidence of COVID-19 vertical transmission.

LITERATURE REVISION

For the bibliographic study, we performed data searches in the MEDLINE bibliographic databases, in the U.S. National Library of Medicine and the National Institute Health (PubMed) interface; Latin American and Caribbean Literature in Health Sciences (LILACS) and Cochrane.

For the search strategy, the keywords were selected using Medical Subject Heading Terms (MeSH). The terms were used to search in the MEDLINE database and later adapted and translated into Spanish and Portuguese, for the search in other databases. The following keywords were used “vertical transmission”, “neonatology”, “COVID-19”, “SARS-CoV-2”.

The inclusion criteria defined for the selection of articles were papers published in English, Portuguese and Spanish, with a theme related to the revision of the gestational and neonatal periods, and with a population referring to the children of mothers with COVID-19. The exclusion criteria refer to studies with animals, studies with humans that do not include the age group and that are not associated with COVID-19. The last 10 years (2010 to 2020) were considered as a time limit for the bibliographic search.

In order to eliminate duplication of articles, the documents were ordered by title and authors, excluding those that appeared more than once (PubMed and Medline, PubMed and Lilacs were the same references). For the selection of studies, we ran a review of titles and abstracts. After the first review, we selected 30 papers from the PubMed database and none from Cochrane. Subsequently, we fully evaluated the texts, and excluded 16 papers, selecting 14 articles from PubMed.

Discussion of the papers

One of the first studies, carried out by Dong et al. (2020) suggested the possibility of vertical transmission based on virus behavior. The study evaluated a newborn, born by cesarean delivery, son to a mother with COVID-19, who had high levels of IgM, IgG and inflammatory cytokines hours after delivery. The high levels of IgM in newborns strongly suggest the possibility of vertical transmission, since the virus does not cross the placenta. The results of nasopharyngeal swab RT-PCR were repeatedly negative and the newborn remained asymptomatic[11].

Pennfield et al. (2020) evaluated placental samples and amniotic membranes of pregnant women diagnosed with COVID-19 considered severe in the peripartum period. Placental and amniotic membrane swabs were performed on 11 patients, and SARS-CoV-2 RNA was found in samples from three patients, with newborns with negative and asymptomatic RT-PCR tests from the first to the 5th day of life. Even without clinical signs that corroborated vertical transmission, such as newborn contamination, the findings of viral RNA in placenta and membrane samples suggest vertical exposure[12].

Such evidence encourages studies to investigate the virus transmission pathway, transplacental or during the intrapartum period, since viral particles of SARS-CoV-2 were isolated from samples of the upper airways and anus of newborns, children from mothers with COVID-19 symptoms early on - the second and fourth days of life. These findings raise a range of questions, given that the test collected by anal and nasopharyngeal swab technique occurred after the newborn’s exposure to maternal fluids during the intrapartum period, with other possibilities of contagion besides the transplacental route[9].

It is difficulty to characterize the vertical transmission of SARS-CoV-2, since some authors reported only the presence of specific IgM antibodies[11], while others detected viral particles; however, it does not specify its origin[9,12]; thus, a systematization of neonatal transmission diagnosis was proposed. The system by Shah et al. (2020) proposes five categories: confirmed transmission, probable, possible,

improbable and uninfected. The first and last categories are considered absolute and confirmatory. To fit into a category, the classification system takes into account the symptoms and results from maternal tests, the clinical status of the newborn at birth and the results of neonatal tests[13].

Based on this classification, Vivantini et al. (2020) conducted a study that proved the transplacental transmission of SARS-CoV-2. The study describes a pregnant woman who has been shown to be infected and symptomatic, who underwent a cesarean section with intact amniotic membranes. Samples of amniotic fluid, blood and bronchoalveolar lavage of the newborn were collected, together with samples from oropharyngeal and rectal swab after cleaning, in the first hour of life. The placenta was also assessed for viral presence. All samples were positive for SARVS-CoV-2.

According to the Maternal-Fetal-Neonatal Infection Classification System SARS-CoV-2, a neonatal congenital infection is considered certain when viral particles are detected in the amniotic fluid before rupture or in the newborn's blood early in life, hereby classified as vertical transmission[3]. Not only was transplacental transmission evident, but the study still describes nonspecific symptoms of the newborn during the second day of life, such as irritability, axial and opisthotonous hypertonia, with posterior magnetic resonance imaging demonstrating bilateral gliosis of the deep white periventricular and subcortical matters. These images are similar to those found in adult patients who have vascular inflammation due to SARS-CoV-2[3,14].

In a literature review, Rasmussen et al. (2020) showed no *in utero* transmission[15] while Yuanqiang et al. (2020) and Procianoy et al. (2020) considered it important to have more evidence to assess vertical transmission[16,10]. Peng et al. (2020) followed a premature newborn with negative tests, son to a mother with COVID-19[17], and Liu et al. (2020) followed 19 newborns, children of mothers positive for COVID-19, all with negative results[18]. Table 1 shows the summary of the articles selected for this review.

CONCLUSION

The current COVID-19 pandemic raises the need for knowledge about the impact of SARS-CoV-2 on the health of humankind globally, in the short, medium and long term. To date, little evidence has been reported on the possibility of vertical transmission of the disease.

Some studies have shown that vertical transmission is possible and its classification criteria are clearly proposed. Others show that the potential for intrauterine vertical transmission of COVID-19 in the first and second quarters is still unknown. Fetal and neonatal repercussions were suggested when the disease was acquired in the third trimester of pregnancy. Some authors found negative samples by RT-PCR techniques in different materials collected from newborns, children of mothers with confirmed COVID-19. Whereas there is evidence of positive serology (IgM and IgG) in the blood of a newborn child born to a mother with confirmed COVID-19.

In this sense, high-quality studies are paramount to clearly demonstrate the possibility of vertical transmission of COVID-19 and the risks of repercussions of serious infection in pregnant women and their babies. Thus, some studies reinforce the importance of monitoring newborns, children of mothers who have had COVID-19 confirmed, regardless of the gestational period, the intensity of clinical manifestations or even if asymptomatic, as these may present an unknown arsenal of future impairments, secondary to infection itself or as a consequence of maternal inflammatory reactions found during SARS-CoV-2 infection.

Chart 1. Summary of the articles selected for review: vertical transmission COVID-19.

Reference	Title	Study type	Main results
1. Chen H, et al.[7] Lancet; 395(10226): 809-815, 2020 03 07.	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	Retrospective	6 newborns born to mothers with COVID-19 had samples of amniotic fluid, umbilical cord blood, smear of the neonatal throat and breast milk evaluated for SARS-CoV-2, and all samples were negative for the virus.
2. Dong L, et al.[11] JAMA. 2020; 323 (18): 1846-1848	Possible vertical transmission of SARS-CoV-2 from a infected mother to her newborn	Case reports	Presence of IgM in the newborn's blood, with negative swabs, suggesting possible transplacental contamination.
3. Duran P et al.[19] Rev Panam Salud Publica. 2020 Apr 27;44	COVID-19 and Newborn Health: Systematic Review	Review	Given the scarcity of studies, vertical transmission cannot be confirmed or excluded at this time.

Continued **Chart 1.**

4. Liu et al.[18] Front Med; 14(2): 193-198, 2020 Apr.	Clinical characteristics of 19 neonates born to mothers with COVID-19	Case series	19 neonates were included in the study. In this, 10 mothers were confirmed with COVID-19 by RT-PCR with positive SARS-CoV-2 in the throat swab and 9 mothers were clinically diagnosed with COVID-19. The RT-PCR of SARS-CoV-2 in the throat swab, urine and feces of all neonates was negative. The RT-PCR of SARS-CoV-2 in breast milk and amniotic fluid was also negative.
5. Muhidin S et al.[20] Arch Acad Emerg Med. 2020 Apr 15;8(1):e49	Analysis of Maternal Coronavirus Infections and Neonates Born to Mothers With 2019-nCoV; A Systematic Review.		Pregnant women at the end of pregnancy had clinical manifestations similar to non-pregnant women. It appears that the risk of fetal distress, premature birth and premature rupture of membranes increases with the onset of COVID-19 in the third trimester of pregnancy. There is also no evidence of intrauterine and transplacental transmission of COVID-19 to the fetus in the third trimester of pregnancy.
6. Penfield C, et al.[12] Am J Obstet Gynecology MFM, 2020	Detection of SARS-COV-2 in Placental and Fetal Membrane Samples	Cohort	The presence of viral RNA in 3 of 11 placentas/ membranes evaluated, suggested the possibility of viral exposure.
7. Peng, Z., et al.[17] J Infect Public Health; 13(5): 818-820, 2020 May.	Unlikely SARS-CoV-2 vertical transmission from mother to child: A case report	Case report	Female preterm newborn was born to a mother with confirmed COVID-19. She had mild respiratory distress, requiring continuous positive airway pressure for a short period. All tests (nucleic tests of SARS-CoV-2 of the throat and anal swab, serum, bronchoalveolar lavage fluid and urine) were negative.
8. Procianoy RS, et al.[10] J. pediatr. (Rio J.) ; 96(3)May-June 2020	Neonatal COVID-19: little evidence and the need for more *information*.	Editorial	Little evidence and need for further information.
9. Rasmussen AS, et al.[15] Am J Obstet Gynecol Maio de 2020; 222 (5): 415-426	Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know	Review	There was no evidence of *in utero* transmission in severe acute respiratory syndrome or Middle East respiratory syndrome.
10. Vivantini A, et al.[3] Nature Research, 2020. Under Review.	Transplacental transmission of SARS-CoV-2 infection	Case report	They showed transplacental transmission, according to the classification of Shah et al. (2020). He described neonatal neurological findings compatible with COVID19.
11. Yang P, et al.[21] J Clin Virol . 2020 Jun;127:104356	Clinical Characteristics and Risk Assessment of Newborns Born to Mothers With COVID-19.	Case series	7 newborns born to mothers infected with SARS--CoV-2. PCR- negative in all cases.
13. Zeng, L., et al.[9] JAMA. 2020.	Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China	Cohort	3 of 33 newborns had early and oligosymptomatic SARS-CoV-2 infection. However, they did not determine the source of the infection.
14. Zhu, H, et al.[8] Transl Pediatric. 2020. 9. 51-60.	*Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia.*	Retrospective	There is a possibility of adverse effects of perinatal COVID-19 infection in newborns, such as premature labor, fetal distress, respiratory distress, thrombocytopenia due to abnormal liver function and death. Currently, vertical transmission of COVID-19 is not reported.

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