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REVIEW ARTICLE

Vertical transmission of Covid-19. What does the evidence say?

Transmisión vertical de COVID-19. ¿Qué dice la evidencia?

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What do we know about the subject matter of this study?

The SARS-CoV-2 infection continues to have worldwide consequences. The effects of infection during pregnancy are an evolving question, as is vertical transmission of the virus and its consequences in the newborn.

What does this study contribute to what is already known?

This provides an approximation based on the published literature, that vertical mother-to-child transmission is possible but infrequent. However, prospective cohort studies are needed to draw more concrete conclusions regarding vertical transmission and its consequences.

Abstract

Vertical transmission of SARS-CoV-2 from the infected mother to the newborn is still uncertain and the definitive answer is under evaluation. The objective of this review was to evaluate the evidence available in the literature regarding whether the pregnant woman infected by SARS-CoV-2 represents a potential risk of vertical transmission to the fetus and/or newborn. **Material and Method:** A scoping review was performed using Science Direct, PubMed, and Cochrane library to search for research papers. Inclusion criteria: published studies of pregnant mothers with COVID-19, with perinatal outcomes reported in the first 72 hours after birth. **Results:** 569 studies were found; 65 of them were repeated. Therefore, 504 were evaluated, of which 460 were excluded. Finally, 42 research papers that met the inclusion criteria were analyzed. 334 pregnant women with COVID-19 and 335 newborns were described; of which 20 presented SARS-CoV-2 infection confirmed by Polymerase chain reaction (PCR) from nasopharyngeal swab. Of these, 18 were identified in the first 48 hours after birth and 12 presented with symptoms. The most frequent route of delivery was cesarean section in 76.2%, and the gestational age range of the newborns was between 26 and 40 weeks. In 86.8% of the cases, mother-child pairs were isolated. **Conclusion:** Vertical transmission of COVID-19 is possible, although infrequent. Prospective studies are required to establish the possibility of *in utero* maternal-fetal transmission and its consequences.

Keywords:
SARS-CoV-2;
COVID-19;
Vertical Transmission;
Newborn

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Introduction

In early December 2019, several cases of pneumonia of unknown origin emerged in Wuhan, Hubei Province, China. Most of these patients reported having been to the Wuhan seafood wholesale market that sold various species of live animals[1]. The disease spread rapidly to other parts of China and other countries around the world[2]. On January 7, 2020, the World Health Organization (WHO) named it as the 2019 novel coronavirus (2019-nCoV), and on March 11, 2020, it was declared as a pandemic[3]. The first case detected in Chile was confirmed on March 3, 2020, and the country entered a Phase 4 health emergency on March 16. As of August 31, 411,726 people had been infected in Chile, of which 11,289 patients died[5].

The disease caused by the 2019-nCoV[6] is a highly contagious disease for all susceptible age groups[6]. However, people with comorbidities or those over 65 years of age are more likely to develop a severe form of the disease[7]. It has been observed that children apparently have reduced acute illness severity[8,9].

At the time of this study, 7 coronavirus species have been identified, including the latest, SARS-CoV-2, which causes disease in humans[10]. Of these, the Severe Acute Respiratory Syndrome virus (SARS-CoV) and the Middle East Respiratory Syndrome virus (MERS-CoV) were identified as causative agents of severe respiratory disease in outbreaks of interspecies infections[1, 10].

This virus is transmitted from person to person, both in symptomatic and asymptomatic patients[11]. Generally, transmission occurs through droplets produced by breathing, talking, coughing, singing, and aerosol particles[11,12]. Aerosol-droplets mediated transmission increases especially in specific circumstances, as occurs during intubation, endotracheal aspiration, etc.[11,12]. However, there is evidence that there may be intestinal infection and excretion through feces, increasing the risk of hand-to-mouth infection[12,13]. Therefore, prevention measures are essential for preventing its spread.

In newborn patients, horizontal transmission of the virus has shown to occur similarly to other age groups[13], however, these patients are also at risk of vertical transmission. This mechanism of transmission remains unclear and requires further study, although there are reports that suggest and/or confirm this type of transmission[14,15,16].

Since the beginning of the pandemic, some cases of neonatal SARS-CoV-2 infection have been reported, the earliest being at 16 and 30 hours after birth[16,17]. It should be noted that most of the described cases of vertical transmission have occurred during the third trimester of gestation. However, the potential effects of infection in the first and second trimesters of pregnancy on the fetus are unknown.

Based on the available evidence and the gaps in the literature so far, regarding the effects of the virus on the fetus and newborn in the possible vertical transmission, we pose the following research question: What is the evidence regarding the possibility of vertical transmission from pregnant women infected with SARS-CoV-2 to fetuses and newborns during the COVID-19 pandemic?

The objective of this review was to evaluate the evidence available in the literature as to whether pregnant women infected with SARS-CoV-2 can transmit the infection vertically to the fetus and/or newborn.

Material and Method

A scoping review[18] was carried out of the existing literature to date. The search engines Science direct, Pubmed, and Cochrane library were used to search for research papers published between January 1 and August 31, 2020. The controlled terms "Infant, Newborn", "Neonatal", "Pregnancy", joined with the Boolean operator OR were used as the population; the controlled terms "Coronavirus", "COVID-19", and "SARS-CoV-2", joined with the operator OR, were used as the intervention; and the controlled terms "Transmission" and "Vertical Transmission", joined with the operator OR, were used as the results. The population, intervention, and results were joined with the Boolean operator AND to create the final search equation. In addition, the controlled term "Severe Acute Respiratory Syndrome Coronavirus 2" was used in the search equation in the Science Direct database, obtaining 564 studies. We also included five additional studies, which were sent by the lead authors to the investigators of this review. (Figure 1)

Inclusion criteria were peer-reviewed publications in English or Spanish of pregnant patients with COVID-19 confirmed by PCR for SARS-CoV-2 and/or compatible chest CT scan and perinatal outcomes described in the study, and infection of the newborn of an infected mother before 72 hours postnatal period. Exclusion criteria were absence of records of neonatal outcomes in mothers infected with SARS-CoV-2 and unpublished maternal and/or neonatal case reports, or without peer control. Review, record, and analysis were performed by the two researchers.

In the studies evaluated, the following were recorded: pregnant women positive with COVID-19; type of delivery; number of newborns; real-time PCR tests for SARS-CoV-2 by nasopharyngeal swab from mother and newborn in the first 72 hours postnatally, and later during hospitalization. PCR for SARS-CoV-2 was as-

sessed in the placenta, amniotic fluid, cord blood, and breast milk. Immunoglobulin G and M levels and response curves from newborns were also recorded. The medical approach with the mother-child pair and the clinical evolution of the newborns infected with SARS-CoV-2 were recorded. Data were analyzed qualitatively, describing results in percentages and frequencies. Since this was an exploratory systematic review, there was no risk of bias assessment.

Results

We found 569 studies, of which 65 were repeated, resulting in 504 titles and/or abstracts. Subsequently, they were evaluated to determine their relevance to the study, excluding 460. Of the 44 studies to be assessed, 2 were excluded due to language limitation (Mandarin Chinese). Finally, 42 research papers were analyzed (figure 1).

Of the studies analyzed[16-17, 19-58], 97.6% were case series or case reports, except for a case-control study published by Yang, H. et al.[20]. These studies describe 334 pregnant patients with COVID-19 confirmed by PCR for SARS-CoV-2 and/or chest CT scan and 335 newborns, of which 20 had SARS-CoV-2 infection, confirmed by PCR (table 1).

Of the 334 pregnancies, the route of delivery was recorded in 308 (92.2%). The 76.3% (235/308) were cesarean section and 23.7% (73/308) vaginal delivery. The gestational age range of the newborns evaluated was between 26 and 40 weeks. Of the 334 newborns born to mothers with COVID 19, there is only one published case of fetal death[29].

Regarding the medical approach with the mother-child pair, this was recorded in 52.2% (175/335) of the

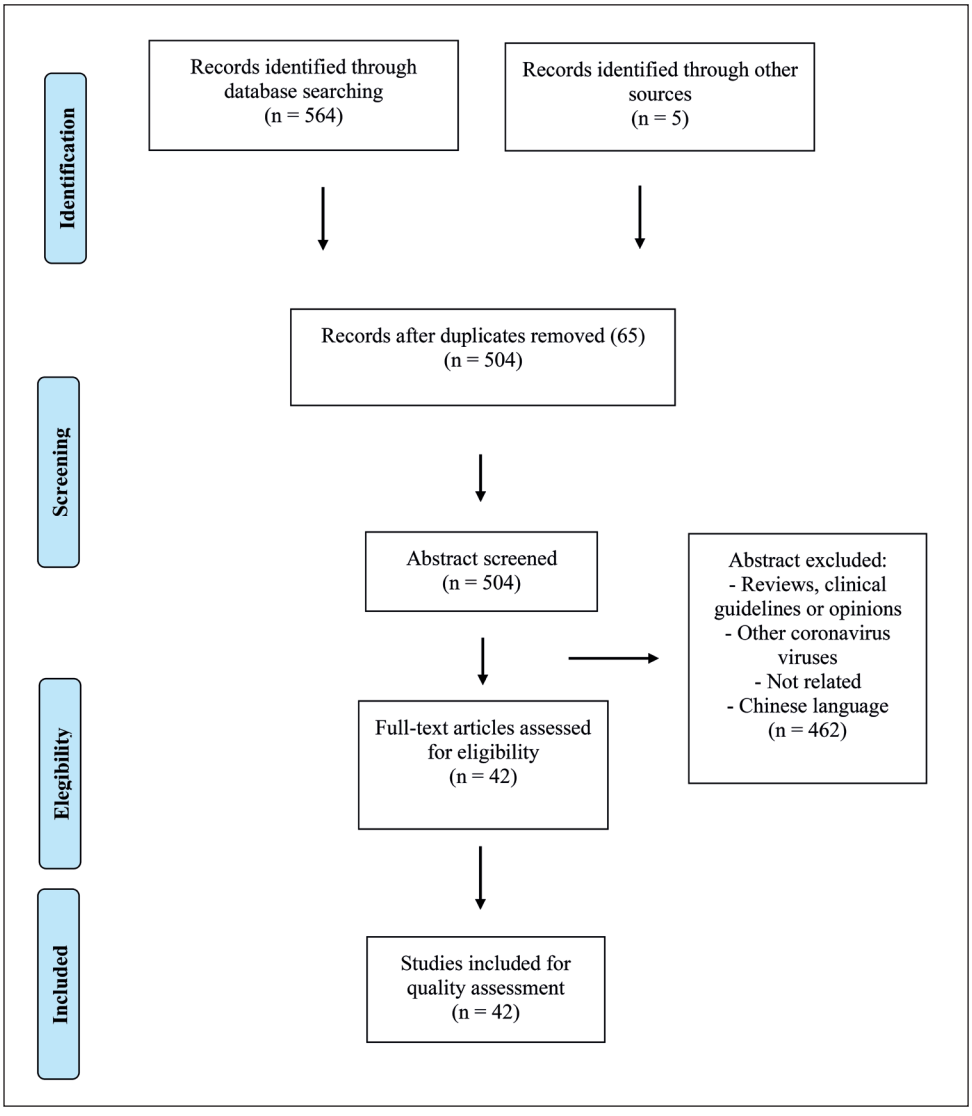

Figure 1. Flow chart of the study selection

cases. In 86.8% of the cases, the newborn was isolated from its mother. In 13.2%, sharing room and breastfeeding of the child was allowed, using personal protection measures, such as hand washing before breastfeeding and use of a face mask. (Table 2)

There were 20 newborns with confirmed COVID-19, accounting for 5.9% of the sample, 18 of them had positive PCR for SARS-CoV-2 in the first 48 hours postpartum. Of these 20 newborns, 60% (12/20) presented some symptomatology. The most frequent signs and symptoms were fever (35%), respiratory distress (30%), and lethargy or irritability (15%). One newborn presented neonatal depression secondary to maternal anesthesia. No neonates died from COVID-19 in this review. (Table 3)

Of the total pregnancies described, the PCR for SARS-CoV-2 in amniotic fluid, placenta, and/or breast milk was performed in 17.9% (60/334) of the newborns. Only 3 patients presented positive results in placental tissue, cord blood, or amniotic fluid. (Table 4)

6 neonates had positive results for immunoglobulins, of which 2 presented increased IgM in blood, but with negative PCR for SARS-CoV-2.

Discussion

In this review, in all newborns who tested positive, SARS-CoV-2 infection was detected during the first 72 hours postpartum. The mechanism of infection was unclear, and it is not possible to determine the exact time of transmission, but it suggests vertical transmission. This transmission could have occurred *in utero* (transplacental infection), during delivery by ingestion or aspiration of cervicovaginal secretions, or during postpartum through breastfeeding[30].

Of the 20 newborns positive for SARS-CoV-2, 18 (90%) were diagnosed through nasopharyngeal swabs before 48 hours postnatal and all of them were completely isolated from the mother since birth, suggesting that it was a vertical and not horizontal transmission. Among these newborns, the case reported by Vivanti, AJ. et al[56] stands out as a confirmed case of transplacental transmission of SARS-CoV-2, since there was positivity in nasopharyngeal PCR samples in the newborn, in the placenta, and confirmed viraemia in maternal blood. The neonate presented neurological alterations on physical examination and imaging[56].

In most of the studies reviewed, pregnant women infected with SARS-CoV-2 had mild to moderate symptoms. However, it should be considered that this is an evolving disease with a small number of cases, so do not draw definitive conclusions.

In studies of pregnant mothers infected with other coronaviruses, such as SARS-CoV, significant maternal mortality was reported, reaching up to 25%[60]. On the other hand, in mothers infected with MERS-CoV, there was 27% of fetal mortality and 27% on average of preterm delivery[61].

Because most case reports (96.5%) were newborns born to mothers with COVID-19 during the third trimester of pregnancy[16-17, 19-58], it is plausible to postulate that the time interval from the clinical manifestation of SARS-CoV-2 infection to the time of delivery is relatively short[16-17, 19-58]. The placental barrier could temporarily delay the transfer of the virus from the mother to the fetus, however, it has not yet been determined whether there may be a greater risk of vertical transplacental transmission when SARS-CoV-2 infection occurs in the first or second trimester of pregnancy since there is a longer time interval of maternal infection[62]. It also remains to be clarified whether earlier maternal infection could have harmful effects on the fetus.

The novel coronavirus uses the angiotensin-con-

Table 1. Studies evaluated with COVID-19 mothers and their newborns

Study design	Nº pregnant women diagnosed with COVID-19	Nº total newborn	Nº newborn diagnosed with COVID-19
Case control 1* (20)**	13	14	0
Case report 18* (16,21,24,26,28,30,35,37,39-43,53-54,56-58)**	20	21	7
Case series 23* (17,19,22-23,25,27,29,31-34,36,38,44-52,55)**	301	300	13
Total	334	335	20

*Number of publications according to study design. **( ) Reference of each study.

Table 2. Medical approach of the mother and newborn

Medical approach	N° newborn
Isolation from mother	152 (16, 17*, 20,23-28,30,32,36-38,40-44, 46-47*,52,55-58)**
Joint mother and child accommodation, with personal protection measures	23 (17*, 21-22,47*,53-54)**

*Zhang, ZJ. et al.[17] and Patané, L. et al.[47] report one newborn in shared accommodation and the rest in isolation from their mother. **( ) Reference of each study.

verting enzyme 2 (ACE-2) to enter the host cell and has a low expression during the first trimester of pregnancy, increasing from week 16 to a maximum at week 24, when it is expressed significantly in the placenta and fetal organs such as heart, liver, and lungs[12,13]. The increase and higher expression of this receptor in the second trimester of pregnancy would increase the likelihood of vertical transmission[13].

Transplacental passage of SARS-COV-2 has been identified through PCR testing in placental tissue, as well as in other fluids, such as cord blood, amniotic fluid, and breast milk. In this review, positivity for this novel coronavirus was observed in 4 samples of placental tissue, 4 of amniotic fluid, and 2 in cord blood[41,45,56,58].

In this review, the delivery route was by cesarean section in most cases (76.2%), despite that there is no standard that justifies the indication for cesarean section in mothers with confirmed COVID-19[63].

Dong, L. et al[26] reported the case of a newborn with elevated levels of IgM anti-SARS-CoV-2 antibodies born to a mother with confirmed COVID-19. In parallel, Zeng, H. et al[27], in mothers with confirmed SARS-CoV-2 disease, reported a series of 6 newborns, of which 4 were IgG positive, one IgM positive, and the last one with both immunoglobulin measurements positive. In both studies[26,27], all newborns had negative nasopharyngeal PCR for SARS-CoV-2. It is important to consider that when specific IgG and IgM antibodies

Table 3. Clinical symptoms of the 20 newborns with COVID-19

GA (weeks)	Clinical symptoms *
33	Neonatal depression secondary to maternal anesthesia[16]
39	Respiratory distress[17]
N/E	Fever[17]
40	Fever and lethargy[25]
40	Vomiting, fever and lethargy[25]
31	Respiratory distress[25]
N/E	Respiratory distress[31]
38	Fever and feeding difficulties[41]
38	Fever and respiratory distress[46]
35	Thermoregulation and feeding difficuties[54]
35	Respiratory distress, irritability, and hypotonia[56]
34	Fever and respiratory distress[57]
40	Asymptomatic[17]
37	Asymptomatic[26]
N/E	Asymptomatic[31]
N/E	Asymptomatic[31]
37	Asymptomatic[47]
35	Asymptomatic[47]
40	Asymptomatic[52]
32	Asymptomatic[58]

*Reference to studies.
**All newborns had a favorable course of the disease. N/E: not specified; GA: Gestacional age.

Table 4. Positive RT-PCR SARS-CoV-2 samples on other tissues.

Study design	No. of patients with evaluation of other tissues	Positive neonatal throat swab samples < 48 hours	Positive breast-milk samples	Positive placental samples	Positive amniotic fluid samples	Positive umbilical cord samples
Case series (19,23,30,32,34,45)*	44	1	0	1	2	0
Case report (24,28,35,37,40,41,42,53,54,57,58)*	11	4	0	3	2	2
Total	55	5	0	4	4	2

*( ) Reference to studies.

are determined as a method of detecting viral infection, it is necessary to observe the variation of these antibodies over time[64]. The study by Zeng, H et al[27], which identified elevated levels of IgM in 2 newborns born measured immediately postnatally, suggests the possibility of vertical transmission *in utero*, despite that the neonate presented a negative PCR by nasopharyngeal swab since this immunoglobulin cannot cross the placental barrier due to its high molecular weight[27].

Regarding breastfeeding, this review does not present results that allow us to rule out infection by this route since not all infants infected by SARS-CoV-2 were screened for this novel coronavirus in breast milk. Those newborns that were tested during the first 72 hours postpartum had negative results[23,30,34,35,42]. It can be speculated that, due to the high concentration of immunological factors present in breast milk during the first week of breastfeeding, viral inhibition or neutralization may occur and thus prevent transmission of SARS-CoV-2 through this route in the postnatal period. Transmission of maternal infection to the neonate may not only be limited to the transmission through milk, but may also occur through other contaminated fluids, which may be present during the breastfeeding period, such as blood (cracked nipples), sweat, or respiratory droplets[65].

In this review, the medical approach with the mother-child pair was variable, which is consistent with the current lack of agreement worldwide on this issue. The WHO suggests shared room (mother-child), without suspension of breastfeeding in both suspected and confirmed cases[66], in contrast, in China is indicated immediate separation of the newborn from her/his mother after birth and breastfeeding is not allowed[66]. The American Academy of Pediatrics suggests the separation of mother and child and to prefer expressing breast milk[66]. The American College of Obstetricians and Gynecologists and neonatal and perinatal societies of the European Union recommend that, in cases of asymptomatic mothers or mothers with mild symptoms, mother and child can share room and the child can be breastfed, maintaining strict measures of hand washing and use of masks[67,68].

In Chile, the recommendation of the Chilean Society of Pediatrics suggests that in the case of a mother and newborn with confirmed COVID-19, share room and use of personal protective equipment with standard measures, recommending the same in the case of a mother with suspected or confirmed COVID-19 and a newborn with negative or pending PCR test result, or an asymptomatic mother or one with mild symptoms[69]. However, in the case of a moderately to severely symptomatic mother, it is suggested that the newborn be isolated from the mother in the neonatal unit until discharge, with expressed breast milk[69].

Current evidence indicates that the risk of vertical transmission of SARS-CoV-2 is low. However, it has been described that between 42 and 93%[15] of pregnant women with COVID-19 are asymptomatic and not all are tested; therefore, there may be an underreporting of vertical infection of the newborn, since a significant percentage of neonates may also be asymptomatic[14]. According to the data of this review, the percentage of vertical infection by SARS-CoV-2 was 5.9%, which is consistent with that published by Kotlyar, AM. et al.[70] (3.2%).

This review has some limitations. Since most of the studies analyzed were about mothers infected with SARS-CoV-2 in the third trimester of pregnancy and not in the first or second trimester which could present different results. In addition, they correspond mostly to mothers with symptoms and not to all pregnant women, many of whom are asymptomatic, therefore, they could be underrepresented and thus the risk of vertical transmission could be different. This review is also based on observational case reports or case series, some of which have incomplete maternal, perinatal, and postnatal data.

The strengths of our review are based on that most mothers and all newborns were diagnosed by PCR by nasopharyngeal swab, which is considered the gold standard test. In addition, this review reports PCR tests performed in infants before 72 hours postnatally and all of them had history of immediate separation from their mothers after delivery. This significantly decreases the likelihood of possible horizontal transmission.

Conclusions

Vertical mother-to-child transmission is possible, although rare, and the timing of SARS-CoV-2 transmission is currently unclear. Infection of the neonate would generally be mild with a good prognosis. Most studies are serial publications and case reports, not prospective cohort studies.

Most publications are from mothers infected with SARS-CoV-2 during the last trimester of pregnancy, and what happens with infection earlier in pregnancy is unknown at this time.

Current evidence suggests that the risk of vertical transmission is low, but this could change as all pregnant mothers and their newborns are tested.

Prospective multicenter studies are required, with complete analysis of all possible susceptible sources of transmission of SARS-CoV-2 infection, such as the placenta, cord blood, amniotic fluid, and breast milk; real-time PCR of serial nasopharyngeal swabbing of the first postnatal days of the newborn as well as the serological curve of immunoglobulins G and

M in newborns and their mothers, in order to determine certainty the exact mechanism and frequency of maternal-fetal transmission *in utero* and its consequences.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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