

# SYSTEMATIC REVIEW

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# Pregnant women with coronavirus disease 2019 and intrauterine vertical transmission: a systematic review

## Gestantes con enfermedad por coronavirus 2019 y transmisión vertical intrauterina: una revisión sistemática

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## ABSTRACT

**Introduction:** Coronavirus disease 2019, also called COVID-19, is a potentially severe respiratory disease originated by the type 2 coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2). Intrauterine transmission from mother to fetus is a matter of debate. **Objective:** To identify the available evidence of vertical intrauterine transmission in pregnant women with COVID-19. **Methodology:** A systematic review was performed using the terms: "Vertical transmission" AND "COVID-19" OR "SARS-CoV-2" NOT "Review \*". The databases consulted were MEDLINE/PubMed, Science Direct, Clinical Key, LILACS, SciELO, Google Scholar, medRxiv and SciELO Preprints. **Results:** Thirty primary studies met the selection criteria and included 476 pregnant women. Infection was found in 9 neonates (1.9%) in whom pharyngeal swabs were done within 48 hours of birth. In four of them the presence of the virus was not looked for in other maternal tissues and fluids; in the remaining 5 cases, the virus RNA was identified in the placenta of three of them, in two it was found in the amniotic fluid and in one in vaginal secretion. Studies were very heterogeneous, with great variety of the reported population, the number of samples and time of collection in neonates, the lack of sampling in maternal tissues and fluids. **Conclusions:** Vertical intrauterine transmission of SARS-CoV-2 has not been conclusively demonstrated in pregnant women with COVID-19 as the majority of patients with the disease had newborns with negative molecular test (98,1%). The heterogeneity of the studies does not allow to rule out this possibility either.

**Key words:** Coronavirus infections, Vertical infectious disease transmission, COVID-19, SARS-CoV-2.

## RESUMEN

**Introducción.** La enfermedad por coronavirus 2019 (COVID-19) es una enfermedad de las vías respiratorias potencialmente severa, producida por el coronavirus tipo 2 causante del síndrome respiratorio agudo grave (SARS-CoV-2). La transmisión intrauterina de la madre al feto es un motivo de debate. **Objetivo.** Identificar la evidencia disponible de transmisión vertical intrauterina en la gestante con COVID-19. **Metodología.** Revisión sistemática utilizando los términos: "Vertical transmission" AND "COVID-19" OR "SARS-CoV-2". Las bases de datos consultadas fueron MEDLINE/PubMed, Science Direct, Clinical Key, LILACS, SciELO, Google Scholar, medRxiv y SciELO Preprints. **Resultados.** Se identificaron 30 estudios que cumplieron los criterios de selección e incluían 476 gestantes. La infección se encontró en 9 neonatos (1,9%), el hisopado faríngeo en ellos se hizo dentro de las 48 horas del nacimiento. En 4 de ellos no se buscó la presencia del virus en otros tejidos y fluidos maternos, mientras que en los 5 casos restantes se identificó el ARN en la placenta de tres de ellos, en dos se encontró en el líquido amniótico y en uno en el canal vaginal. Los estudios fueron muy heterogéneos; así podemos mencionar la variedad de la población reportada, el número de muestras y momento de la toma en los neonatos, la falta de muestreo en los tejidos y fluidos maternos. **Conclusiones.** La transmisión vertical intrauterina del SARS-CoV-2 no ha sido demostrada de forma contundente debido a que la mayoría de las gestantes con la enfermedad ha tenido neonatos con la prueba molecular negativa (98,1%). Sin embargo, la heterogeneidad de los estudios tampoco permite descartar esta posibilidad.

**Palabras clave.** Infecciones por coronavirus, Transmisión vertical de enfermedad infecciosa, COVID-19, SARS-CoV-2.



## INTRODUCTION

Coronavirus disease 2019 or COVID-19 is a potentially serious airway disease. This disease is originated by the type 2 coronavirus that causes SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)<sup>(1)</sup>.

COVID-19 was first described in late December 2019 in Wuhan Province in the People's Republic of China. From that moment on, SARS-CoV-2 infection spread rapidly to other countries in Asia, Europe and the Americas, with the first case detected in Peru on March 5, 2020. On March 11, the World Health Organization (WHO) officially declared COVID-19 a pandemic<sup>(2)</sup>. As of August 30 this year, more than 200 countries had reported a total of 25 057 670 confirmed cases and about 842 915 deaths; these figures will continue to rise and are updated in real time on the website of the Coronavirus Resource Center of Johns Hopkins University available at: <https://coronavirus.jhu.edu/map.html>

According to the WHO, this virus is transmitted by direct contact with respiratory droplets expelled by infected people when they cough, speak or exhale. It can also be transmitted by indirect contact when the droplets exhaled by the sick person adhere to different objects and surfaces, which are transmitted when a healthy person touches these surfaces and then touches the mucous membrane of the eyes, nose or mouth<sup>(2)</sup>.

The predominant clinical picture is respiratory, which can range from mild compromise in 85% of cases due to involvement of the upper airways (similar to a common cold) to severe and fatal in 5% when it affects the lower airways (complicated pneumonia with acute respiratory distress syndrome - ARDS - and single or multiple organ failure). Other organs or tissues that may also be affected by SARS-CoV-2 include the cardiovascular, neurological, gastrointestinal, and dermatological systems. The lethality can be up to 5% depending on the population group studied. Factors associated with higher lethality include older age, especially from 60 to more years, presence of comorbidities such as high blood pressure, diabetes mellitus, chronic lung disease, obesity, and states of immunosuppression<sup>(1)</sup>.

The diagnosis of COVID-19 is confirmed in an asymptomatic or symptomatic person with a positive result on one of the molecular or genomic tests that detect SARS CoV-2, such as the reverse transcription polymerase chain reaction (RT-PCR)<sup>(3)</sup>.

To date, there is no specific pharmacological treatment to prevent or cure COVID-19, so management of infected patients is symptomatic or through supportive measures, according to the severity of the disease<sup>(3)</sup>.

As the number of infected people increased worldwide, confirmed cases of pregnant women with COVID-19 appeared. Some studies have reported that infected pregnant women do not usually progress to very severe cases. Symptoms are characterized by the presence of fever that is followed by respiratory symptoms such as dry cough, dyspnea, fatigue and / or myalgia and, to a lesser extent, gastrointestinal symptoms such as diarrhea. At present it is not clear whether the lung condition or pattern of pneumonia in infected pregnant women differs from that in the general population<sup>(4)</sup>.

It is well documented, and based on evidence, that transmission of SARS-CoV-19 from human to human is through the airway, although the presence of SARS-CoV-2 has also been found in other fluids and secretions such as blood, feces, cerebrospinal fluid, saliva, tears, semen, and conjunctival secretions. This has led some authors to raise the possibility of fecal-oral transmission<sup>(1,5)</sup>.

There are some reports of altered perinatal outcomes in pregnant women with COVID-19 depending on the trimester when the infection occurred, including miscarriages and preterm deliveries, but in no case was the transmission of the infection from mother to child demonstrated<sup>(5)</sup>.

The vertical intrauterine transmission of COVID-19 remains controversial. Abarzúa<sup>(6)</sup> mentioned that cases of this potential transmission route continue to be reported, such as in China where a newborn born by cesarean section from a mother with confirmed COVID-19 pneumonia tested positive for SARS-CoV-2 in the pharyngeal swab study. Unfortunately, there were no stud-



ies in samples of amniotic fluid, cord blood, placenta or breast milk, which could have clarified the hypothesis about the time of transmission, whether it occurred before delivery or postpartum.

To date, doubts remain about the possibility of vertical intrauterine transmission from the mother with COVID-19 to the product of gestation, so it is necessary to review and analyze the information available. Therefore, a systematic review was carried out to determine if there is scientific evidence of vertical intrauterine transmission in the pregnant woman with COVID-19.

## METHODS

A systematic search of primary studies was done from June 26 to July 30, 2020 using MeSH terms (Medical Subject Headings) in free databases and two preprint repositories, the latter in order to decrease selection bias. Case reports, case series, case-control and cohort studies of pregnant women and neonates with diagnosis of COVID-19 confirmed by molecular test were included. The studies were published in English, Spanish, or Portuguese between December 31, 2019 and July 15, 2020. Duplicate primary papers were excluded, selecting the most updated and of the best scientific quality, COVID-19 cases confirmed by non-molecular tests, and cases of non-intrauterine vertical transmission.

To maximize sensitivity, a search strategy was carried out through databases of international publications: MEDLINE/PubMed, Science Direct, Clinical Key, LILACS, SciELO and Google Scholar; and medical preprints repository: medRxiv and SciELO Preprints. The search was carried out on the title and abstract of the selected database with the following MeSH terms: "Vertical transmission" AND "COVID-19" OR "SARS-CoV-2" NOT "Review\*" OR "Meta-Analysis". The PRISMA guide was followed and registered in the PROSPERO database (registration code: CRD42020193798).

The articles were identified, screened, reviewed, selected and analyzed by the researchers. In case of any disagreement about any article or content of this, it was decided to accept it by simple majority with the support and guidance from the more experienced researcher. The data collected were: bibliographic source, type of study, pregnant woman's age, weeks of

gestation (trimester of pregnancy), pregnant woman's symptoms, pharmacological treatment of the pregnant woman, type of delivery, sex of the newborn, age of COVID-19 diagnosis in the newborn, symptoms in the newborn and presence or absence of SARS-Cov-2 in tissues or fluids related to vertical intrauterine transmission (for example, amniotic fluid and/or membrane, umbilical cord and placenta). If the article was a case report, data were extracted on an individual basis. If the article was a case series, case-control or cohort, the mean was calculated for quantitative variables and the proportion of the total for qualitative variables, in addition to ranges according to data availability.

The primary outcome was the presence or absence of neonatal COVID-19 confirmed by molecular method, due to vertical intrauterine transmission of pregnant women with COVID-19 confirmed by molecular method.

## RESULTS

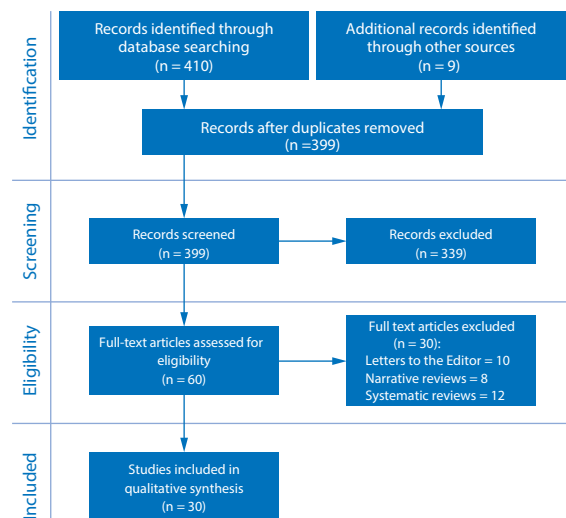
A total of 419 studies were identified from 410 (97.9%) peer review medical databases studies and 9 (2.1%) database studies of pre-published studies. Twenty duplicate articles were discarded during the process, remaining 399 studies for screening. After reading the abstract of the screened articles, 339 studies were excluded, with 60 articles eligible for full-text review. Of these, 30 were excluded for the following reasons: 10 articles were letters to the editor, 8 articles were narrative reviews and 12 articles were systematic reviews. Finally, 30 articles (7-36) were included in the analysis, synthesis and presentation (Figure 1).

The 30 articles included reported 476 cases of pregnant women with confirmed diagnosis of COVID-19 with their respective neonates (477 due to a twin pregnancy). Thirteen studies were case reports (13 patients), 7 observational studies (190 patients), 7 case series (144 patients), and 3 cohort studies (129 patients), as shown in Table 1.

The maternal age range fluctuated between 15 and 45 years. Most cases occurred during the third trimester of pregnancy. The most prevalent maternal symptoms of infection were: fever in 143 cases (30% of cases), cough in 127 cases (26.7%), dyspnea in 29 (6.1%), fatigue in 25



FIGURE 1. FLOW CHART OF THE SELECTION PROCESS OF INCLUDED STUDIES TO EVALUATE THE VERTICAL INTRAUTERINE TRANSMISSIBILITY IN PREGNANT WOMEN WITH CORONAVIRUS 2019 DISEASE ACCORDING TO THE PRISMA GUIDE.



(n = number of studies)

(5.3%), myalgias in 13 (2.7%), and digestive disorders in 11 cases (2.3%), among other symptoms. Asymptomatic pregnant women were 32 (6.7% of cases).

Among the drugs indicated for pregnant women were antivirals, antibiotics, corticosteroids and hydroxychloroquine. The term of pregnancy in most patients was by cesarean section, and only 78 vaginal deliveries (16.4%) were reported.

In 46% of the studies reviewed, the sex of the newborns was not reported, but in the remaining 54%, 68 were males and 53 females. The neonatal age at which the molecular test for the diagnosis of COVID-19 was performed fluctuated between the moment of birth and the 14th day of birth.

In 8 of the 30 included studies<sup>(8,10,19,21,23,29,35,36)</sup>, a total of 9 confirmed positive newborns were reported. In 19 studies of the total, none of the infants showed symptoms of COVID-19 and the remaining 11 studies described various symptoms including tachypnea, fever, vomiting, abdominal distention, liver dysfunction, and neurological symptoms/signs.

In 19 studies, the presence of molecular SARS-CoV-2 in tissues and fluids related to vertical intrauterine transmission was not investigated; in the remaining 11 studies<sup>(10,13,16,23,29-35)</sup> the virus was found in 7 of 19 placentas studied, and only

in 3 of these 7 placentas there was coexistence of neonatal COVID-19. The virus was identified in 2 out of 8 amniotic fluid samples, and in cases of virus-positive placenta it coexisted with neonatal COVID-19. SARS-CoV-2 was identified in 2 out of 9 umbilical cord blood samples and in those cases, there was coexistence with neonatal COVID-19; vaginal mucosa and maternal blood or plasma were also studied.

## DISCUSSION

Despite the time that has elapsed and the increasing number of cases of the disease in pregnant women and the reported cases of probable vertical intrauterine transmission of the disease, this mechanism of transmissibility is still in doubt<sup>(1-5)</sup>.

The objective of this study was to determine if there is scientific evidence of vertical intrauterine transmission in the pregnant woman with COVID-19.

Despite the fact that most cases of pregnant women with COVID-19 have completed their gestation with neonates without confirmed COVID-19 (98.1% or 468 of 477 cases), it is important to take into account some aspects that may condition this result.

Molecular test (RT-PCR) confirms the presence of SARS-CoV-2 and therefore COVID-19, even in asymptomatic patients<sup>(1-4)</sup>. Unfortunately, its accuracy is not 100%, it has high specificity and moderate sensitivity. Despite this, it is considered the gold standard for the moment<sup>(37-39)</sup>. On the other hand, the sensitivity of this test depends on the method and anatomical location for taking the sample as well as the time of evolution of the disease<sup>(37-39)</sup>. For example, if the neonatal swab is done too early or late, the sensitivity may be lower than desired. Therefore, in doubt about the exact moment of the hypothetical neonatal intrauterine infection, the best thing would be to take the sample serially.

Our review found that in 16 studies only one swab was taken and it was within 36 hours of birth and in 2 studies at 72 hours; in 10 studies serial swabs were taken and in the remaining 2 the time of swab taking was not specified. Of the 9 neonates found with positive RT-PCR, two were sampled at birth<sup>(29)</sup>, one at 6 hours<sup>(35)</sup>,



TABLE 1. SUMMARY AND CHARACTERISTICS OF PRIMARY STUDIES ANALYZED TO EVALUATE THE INTRAUTERINE VERTICAL TRANSMISSIBILITY OF PREGNANT WOMEN WITH CORONAVIRUS 2019 DISEASE.

Author and bibliographic reference	Type of study (number of patients)	Age of the pregnant woman	Gestational age	Symptoms of pregnancy	Pharmacological treatment of the pregnant woman	Type of delivery	Sex of the newborn	Neonatal age at the molecular test	Newborn symptoms	Presence of SARS-Cov-2 in maternal fluids and/or tissues
Fan et al <sup>(7)</sup>	Case series (2)	32 years old	37 weeks	Nasal congestion, fever, odynophagia, skin rash	Azithromycin, oseltamivir, methylprednisolone, ceftazidime	Cesarean section	No report	Negative (36 hours)	Fever, abdominal distention	It was not performed
Wang et al <sup>(8)</sup>	Case report	34 years old	40 weeks	Fever	Ganciclovir, abipenem, moxifloxacin, methylprednisolone	Cesarean section	Male	Positive (36 hours)	Asymptomatic	It was not performed
Li et al <sup>(9)</sup>	Case report	30 years	35 weeks	Cough, dyspnea	Lopinavir, ritonavir, methylprednisolone	Cesarean section	Male	Negative (24 hours)	Asymptomatic	It was not performed
Zamanyan et al <sup>(10)</sup>	Case report	22 years old	32 weeks	Dyspnea, myalgia, anorexia, fever, vomiting, cough	Azithromycin, ceftriaxone, lopinavir, ritonavir, oseltamivir, hydroxychloroquine	Cesarean section	Female	Initially negative, then positive (24 hours)	Dyspnea	Amniotic fluid positive, cord blood negative and vaginal discharge negative
Lu et al <sup>(11)</sup>	Case report	22 years old	38 weeks	Asymptomatic	Lopinavir, chloroquine phosphate	Cesarean section	Female	Negative (2 hours)	Asymptomatic	It was not performed
Dong et al <sup>(12)</sup>	Case series (2)	29 years old	34 weeks	Fever, nasal congestion, dyspnea	Oseltamivir, methylprednisolone	Cesarean section	No report	Negative (2 hours)	Asymptomatic	It was not performed
Penfield et al <sup>(13)</sup>	Cohort (34)	30 years	38 weeks	Asymptomatic	Not mentioned	Cesarean section	No report	Negative (24 hours)	Asymptomatic	Placenta: positive in 3 of 11 cases studied
Masmejan et al <sup>(14)</sup>	Case report	31 years old	38 weeks	Cough, dyspnea	Methylprednisolone	Cesarean section	Female	Negative (1 hour)	Asymptomatic	It was not performed
Patané et al <sup>(15)</sup>	Case report	28 years old	36 weeks	Cough, fever	Not mentioned	Cesarean section	Male	Negative (36 hours)	Asymptomatic	It was not performed
Ferraiolo et al <sup>(16)</sup>	Case report	30 years	38 3/7 weeks	Asymptomatic	Did not receive	Cesarean section	No report	Negative (1 at birth - 2 at 24 hours)	Asymptomatic	Placenta: positive
Romagano et al <sup>(17)</sup>	Case series (8)	30.5 ± 9.0 years	31 weeks	Fever (1), cough (6) and dyspnea (7)	Prenatal corticosteroids, hydroxychloroquine, azithromycin, methylprednisolone, ceftriaxone	Cesarean section	Female (4) Male (4)	Negative (24 hours)	Breathing difficulty	It was not performed
Sentilhes et al <sup>(18)</sup>	Observational, retrospective (54)	19-42 years old	37.4 ± 4.7 weeks	Fever (14), cough (36), respiratory distress (22), digestive disorders (9), anosmia (20)	Antivirals lopinavir, ritonavir, antibiotics, corticosteroids, hydroxychloroquine	Cesarean (9) Vaginal (12) Abortion (1) In progress (32)	No report	Negative (In term RN: at birth or day 1 and day 3, in preterm RN: day 7 and day 14)	No report	It was not performed
Pierce et al <sup>(19)</sup>	Cohort (64)	33 years old	30 ± 6 weeks	Dyspnea	Hydroxychloroquine, remdesivir, steroids, antibiotic	Cesarean section (24) Vaginal (8)	No report	32 negative (24 hours), 1 positive (48 hours)	Asymptomatic	It was not performed
Cao et al <sup>(20)</sup>	Retrospective observational (10)	29-35 years old	33-40 weeks	Fever (7), cough (1), chest tightness (1), fatigue (1)	No report	Cesarean section (8) Vaginal (2)	No report	Negative (24 hours)	Asymptomatic	It was not performed





Author and bibliographic reference	Type of study (number of patients)	Age of the pregnant woman	Gestational age	Symptoms of pregnancy	Pharmacological treatment of the pregnant woman	Type of delivery	Sex of the newborn	Neonatal age at the molecular test	Newborn symptoms	Presence of SARS-Cov-2 in maternal fluids and/or tissues
Xiong et al <sup>(21)</sup>	Case report	34 years old	40 weeks	Fever	No report	Cesarean section	No report	Positive (36 hours)	Asymptomatic	It was not performed
Liu et al <sup>(22)</sup>	Observational retrospective (51)	31.9± 4 years	38 weeks	Asymptomatic Symptomatic: fever (4), cough (4)	No report	Cesarean section (48), Vaginal (3)	Female (27), Male (24)	46 negative and 5 false positives (at birth, on days 1 and 5 after birth)	Abdominal distention, vomiting	It was not performed
Chen et al <sup>(23)</sup>	Observational retrospective (9)	26-40 years old	36-39 weeks	Fever (7), cough (4), myalgia (3), sore throat (2), general malaise (2)	Antibiotics, antivirals	Cesarean section	No report	Five negative (36 hours). One positive (36 hours)	No report	Amniotic fluid, umbilical cord blood, breast milk: negative in 6 studied cases
Qiancheng et al <sup>(24)</sup>	Retrospective observational (28)	30 years old (18-41)	38 weeks	Fever (5), malaise (1), cough (7), dyspnea (2), abdominal pain (5)	Antivirals (21) ribavirin (20) and umifenavir (1) Antibiotics (24) cephalosporin (20) and quinolone (4), corticosteroids (4), gamma globulin (3)	Cesarean section (23) Vaginal (5)	No report	Negative (24 - 48 hours old)	No report	It was not performed
Yan et al <sup>(25)</sup>	Case series (116)	30.8 years (24-41 years)	38 weeks (36-39)	Fever (59), cough (33), fatigue (15), myalgia (6), dyspnea (3), diarrhea (1), no symptoms (27)	Antibiotic therapy (109), antiviral therapy (63), steroids (37)	Cesarean section (85) Vaginal (14)	No report	Negative. Does not report age	No report	It was not performed
Peng et al <sup>(26)</sup>	Case report	25 years	35 weeks	Fever, fatigue, shortness of breath	Oral lopinavir, intravenous antibiotics, dexamethasone	Cesarean section	Male	Negative at 2 hours of birth and at day 14	Tachypnea, moaning, periodic breathing	It was not performed
Yang et al <sup>(27)</sup>	Prospective observational (7)	No report	No report	Fever (5), cough (1), abdominal pain (1)	No report	Cesarean section	Male (4) Female (3)	Negative (2-5 days old)	No symptoms (4) Vomiting (1) Complaining (2)	It was not performed
Yin et al <sup>(28)</sup>	Retrospective cohort (31)	31 years old (20-40)	1st quarter (4), 2nd quarter (5), 3rd quarter (22)	Fever (17), cough (15), fatigue (6), dyspnea (8), expectoration (5), diarrhea and vomiting (2), myalgia, anorexia and nausea (3)	No report	Cesarean section (13) Vaginal (4)	No report	Negative. Does not report age	No report	It was not performed
Fenizia et al <sup>(29)</sup>	Prospective observational (31)	30 years (15-45)	No report	No report	Antibiotic (10), antiviral (8), hydroxychloroquine (13)	Vaginal (25) Cesarean (6)	Male (18) Female (13)	2 RN positive at birth	No report	Placenta positive in 2, maternal plasma positive in 2, umbilical cord and vaginal discharge positive in 1; 30 cases were studied
Hsu et al <sup>(30)</sup>	Case report	29 years old	40 weeks	Myalgias	No report	Vaginal	Male	Negative (24 hours old)	No report	Placenta positive



Author and bibliographic reference	Type of study (number of patients)	Age of the pregnant woman	Gestational age	Symptoms of pregnancy	Pharmacological treatment of the pregnant woman	Type of delivery	Sex of the newborn	Neonatal age at the molecular test	Newborn symptoms	Presence of SARS-Cov-2 in maternal fluids and/or tissues
Khan et al <sup>[31]</sup>	Case series (3)	29 years old	37 weeks	Fever (2), cough (3), chest pain (1)	No report	Vaginal	No report	Negative (within 12 hours of delivery)	No report	Umbilical cord blood negative
Zhu et al <sup>[32]</sup>	Retrospective observational (9)	30 years	37 weeks	Fever, cough, diarrhea (9)	Oseltamivir (4)	Cesarean (8) Vaginal (2)	Male (8) Female (2)	Negative (1-9 days old)	Breathing difficulty (6), fever (2), abnormal liver function (2)	Placental tissue, umbilical cord blood, amniotic fluid, vaginal swabs and breast milk: negative
Chen et al <sup>[33]</sup>	Case series (4)	29 years old	37 weeks	Fever (3), cough (2), myalgia or fatigue (2), headache (2)	No report	Cesarean (3) Vaginal (1)	Male (3) Female (1)	Negative (72 hours old)	No symptoms (3) Dyspnea (1)	Placental tissue, umbilical cord blood, amniotic fluid, vaginal swabs and breast milk: negative
Wang et al <sup>[34]</sup>	Case report	28 years old	30 weeks	Fever	Atidol, lopinavir, ritonavir, cefoperazone sodium	Cesarean section	Male	Negative (72 hours old)	Asymptomatic	Amniotic fluid samples, placenta, umbilical cord blood: negative
Vivanti et al <sup>[35]</sup>	Case report	23 years old	35 weeks	Fever, demanding productive cough	No report	Cesarean section	Male	Positive (6 hours old)	Neurological signs and symptoms.	Amniotic fluid, placenta and maternal blood: positive.
Alzamora et al <sup>[36]</sup>	Case report	41 years old	33 weeks	General malaise, fatigue, fever and dyspnea	Corticoids, azithromycin, hydroxychloroquine, oseltamivir	Cesarean section	No report	Positive (16 and 48 hours old)	No report	It was not performed

one at 16 hours<sup>(36)</sup>, one at 24 hours<sup>(10)</sup>, three at 36 hours<sup>(8,21,23)</sup>, and one at 48 hours<sup>(19)</sup> after birth. These findings would show us how relative it can be to use a single sampling as a diagnostic method to demonstrate or rule out vertical transmission.

Wang S et al<sup>(8)</sup> mention that vertical transmission after primary maternal infection can usually occur during intrauterine life through the transplacental route or during delivery by ingestion or aspiration of cervicovaginal secretions, it is for this last reason that it is decided to terminate the pregnancy by cesarean section, which was evident in most of the articles reviewed except for ten articles<sup>(18-20,22,24,25,28-31)</sup> where delivery was by the vaginal route. Six neonates positive for COVID-19 were delivered by cesarean section<sup>(8,10,21,23,35,36)</sup> and in the remaining three the delivery route was not specified<sup>(19,29)</sup>. These results do not allow us to recommend a specific route for the termination of pregnancy to prevent infection in the neonate.

As previously mentioned, the controversial results of the identification of viral RNA in the different maternal tissues and fluids keep the intrauterine transmission mechanism in doubt. To date, reports of SARS-CoV-2 in maternal tissues and fluids have increased. If the virus is found in the placenta, amniotic fluid, or vaginal canal, introduction of this through the neonatal airway would be likely, even if there is no aerosolization. And if we add the duration of fetal exposure to those tissues and fluids, it could be equivalent to exposure to an environmental viral load. The viral RNA was identified in 8 of 14 amniotic fluid samples studied<sup>(10,23,32-35)</sup>; the neonate was COVID-19 positive in two cases; it was identified in 7 of 19 placentas<sup>(13,16,29,30,32-35)</sup> of which three were COVID-19 positive neonates. SARS-CoV-2 was found in a sample of maternal blood or plasma<sup>(29,35)</sup> and it was associated with two COVID-19 positive neonates. In the remaining three positive neonates<sup>(8,19,36)</sup>, the presence of the virus in other maternal tissues or body fluids was not investigated. In some studies, SARS-CoV-2 was looked for in tissues and/or fluids of mothers with COVID-19, and results were negative, as described by some authors<sup>(23,31-34)</sup>.

Despite there being a greater report of probable cases of vertical intrauterine transmission of COVID-19 compared to previous reviews<sup>(40-47)</sup>,



the presence of several factors in the different studies does not allow for definitive conclusions. Among these factors, we can mention the heterogeneity of the reported population (maternal age, gestational age, treatment for COVID-19 received, way of ending the pregnancy), as well as the number of samples and time of collection in the neonates, the lack of sampling of maternal tissues and fluids in most cases.

Among the limitations of this review, it is considered that no studies in other languages and no manuscripts such as letters to the editor were included, and there was a lack of accessibility to all virtual and written databases available.

## CONCLUSIONS

Vertical intrauterine transmission of SARS-CoV-2 has not been conclusively demonstrated in the pregnant woman with COVID-19 because most patients with the disease have not had neonates with a positive molecular test (98.3%). However, the heterogeneity of the studies does not allow ruling out this possibility either in cases where maternal and fetal factors converge. Future more complete and homogeneous studies may shed light on our doubts.

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