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Perinatal transmission with SARS-CoV-2 and route of pregnancy termination: a narrative review*

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ABSTRACT

Objective: Analyze newborns diagnosed with SARS-CoV-2 performed with RT-PCR at birth or during the first days of birth and to look for an association with the route of birth.

Methods: We conducted a comprehensive literature search for newborns diagnosed with COVID-19 using PubMed, LILACS and Google scholar until May 15, 2020, looking for published articles with pregnancy, vertical transmission, intrauterine transmission, neonates, delivery.

Results: There were found 10 articles with a total of 15 newborn infected with SARS-CoV-2 according to positive PCR at birth or in the first days of birth. Eleven newborn birth by cesarean section and 4 vaginally. Of the 11 cases with cesarean section, two presented premature rupture of the membranes. Seven newborns developed pneumonia, of which two had ruptured membranes and one was born by vaginal delivery.

Conclusion: This review shows that there is perinatal or neonatal infection with SARS-CoV-2 by finding a positive PCR in the first days of birth. In addition, that there is more possibility of neonatal infection if the birth is vaginal or if there is premature rupture of the membranes before cesarean section. Vaginal delivery and premature rupture of membranes should be considered as risk factors for perinatal infection.

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SARS-COV-2; vaginal delivery; cesarean section; vertical transmission; perinatal infection

Introduction

Since December 2019, a viral respiratory disease has been described in China and in less than three months a pandemic [1] would be declared. This disease known today as COVID-19 is generated by the SARS-CoV-2 virus [1,2].

The virus has been found in the respiratory tract, feces, serum and in other specimens of the human body [1–3] and the disease has been diagnosed in newborns, adolescents, young adults, older adults, women, men, and women pregnant [2,3].

The evolution in pregnant women is usually mild in nine out of 10 pregnant women, the symptoms are similar to the general population and maternal mortality less than 1% [4,5]. Transmission of the virus from mother to newborn may be by direct contact, but the possibility of transmission by breastfeeding, transplacental and vaginal [3,5–8] has also been studied. Recently, cases of possible vertical transmission have been published, however, there is no conclusive

evidence of such transmission, nor through breast milk [3–8].

Our objective is to analyze newborns diagnosed with SARS-CoV-2 performed with RT-PCR during the first 5 days of birth and to look for an association with the route of birth.

Materials and methods

This research is a systematic review with the following inclusion criteria: case or case series from December 2019 to May 15, 2020 that included pregnant women infected with SARS-CoV-2 and newborns with a positive RT-PCR test at birth or performed in the first 4 days of birth.

We searched the online databases PubMed, LILACS, and Google Scholar for studies that included the established inclusion criteria. We used the following search strategy: (“SARS-CoV-2” OR “COVID-19” OR (“CORONAVIRUS”) AND “pregnancy” AND “vertical transmission,” “maternal-fetal transmission,”

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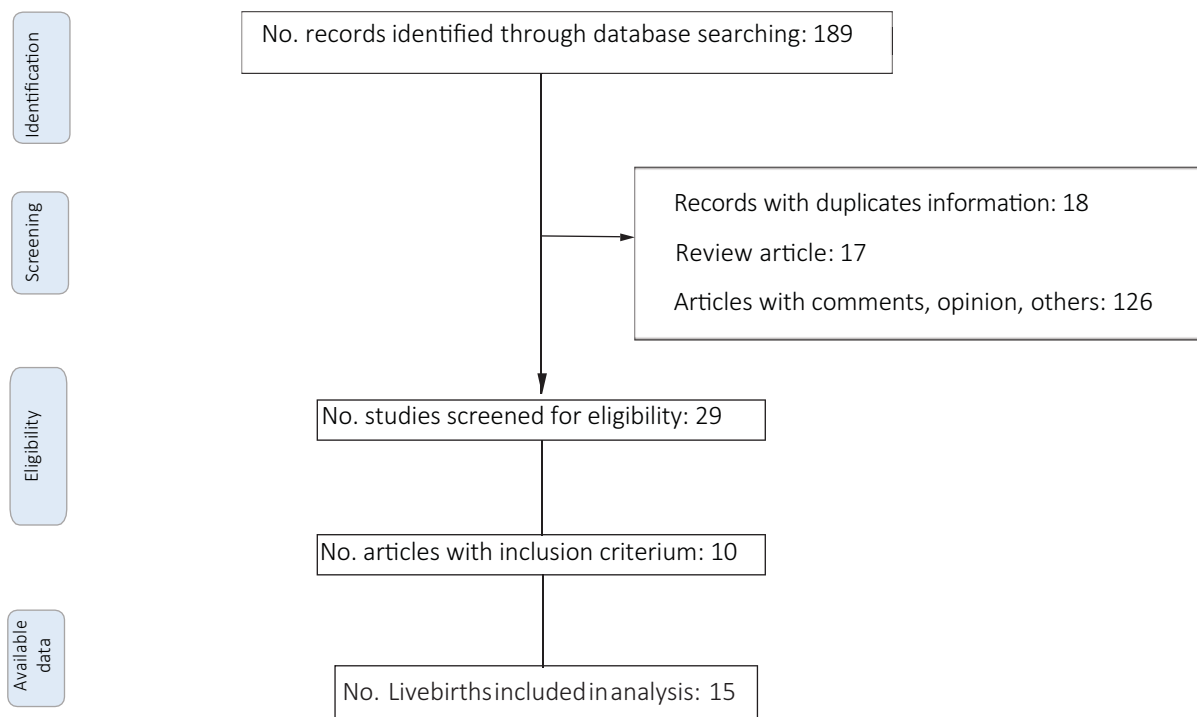


Figure 1. Flow diagram - Summary of evidence search and analysis.

“intrauterine transmission”, “vaginal delivery,” “cesarean section,” “neonates”) with the search limits “human”. In addition, references from review articles, and clinical guidelines were reviewed. There was no language restriction. This research was extended to the references of all the articles in special of review and publications of associations.

The three researchers independently searched, reviewed each article, analyzed each case and exported the relevant data to a data sheet. Also, doubts and discrepancies were resolved in a consensual manner among all.

Results are presented as numbers and percentages.

Results

The initial research found 189 references. After the review, 10 articles meet the inclusion criteria set out in this review, [Figure 1](#). The 10 articles [3,5–13] with the main data for each newborn appear in [Table 1](#).

In total, up to May 10, 2020, we found a total of 15 newborn infected with SARS-CoV-2 according to positive PCR at birth or in the first days of birth, [Table 1](#). Eleven newborn birth by cesarean section and 4 by natural birth. Of the 11 cases with cesarean section, two presented premature rupture of the membranes. They are reported with a clinical finding of pneumonia in 7 of the 15 neonates.

The PCR analysis for SARs-CoV-2 was performed in three placenta (1 natural delivery, 2 cesarean section) and one are reported as positive, the rest of the placenta were not analyzed. In three cases analysis was performed at the vaginal secretions (one vaginal delivery, two cesarean section) and one case was reported positive; also, the case of vaginal delivery is positive at the perianal area and in feces, [Table 1](#). In only one case of the 15 was amniotic fluid PCR analyzed and it was reported positive, this patient ended by cesarean section.

Of the 15 infants with PCR in this study, 4 were born by vaginal delivery and two of the 11 who were born by cesarean section had premature rupture of the membranes; therefore, 6 newborns were exposed to possible vaginal-perianal contamination. Seven newborns developed pneumonia, of which two had ruptured membranes and one was born by vaginal delivery.

The frequencies of cesarean section with COVID-19 are around 80–90% according to the literature [3–11, 14] and this review reports 15 cases of perinatal SARS-CoV-2 infection and 4 of them are born by natural childbirth; If there is no association between the route of birth and perinatal infection, there must be an 8–9:1 ratio between those infected born by cesarean section and those born by natural childbirth. The ratio found in this study is 4:1; is twice the risk of neonatal SARS-CoV-2 infection at vaginal birth.

Table 1. Articles with newborn positive PCR for SARS-CoV-2 with some maternal and neonatal data.

Author	Journal	Country	Case	Gestational age	Cesarean Section	Vaginal Delivery	PROM	Neonatal pneumonia	PCR at other specimens
Zeng L [3]	JAMA Pediatr	China	1	40	Yes	–	Yes	Yes	NR
		China	2	40.4	Yes	–	No	Yes	NR
		China	3	31.2	Yes	–	Yes	Yes	NR
Zamaniyan M [5]	Prenat Diagn	Iran	1	30.2	Yes	–	No	No	Positive amniotic fluid, Negative umbilical cord blood and vaginal secretions.
Ferrazzi E [6]	BJOG	Italy	1	>37	Yes	–	NR	Yes	NR
		Italy	2	>37		Yes	NR	No	
		Italy	3	>37		Yes	NR	No	
Wang S [7]	Clin Infect Dis	China	1	40	Yes	–	No	Yes	Negative in placenta, cord blood and breastmilk
Zhang ZJ [8]	Eur Respir J	China	1	40	Yes	–	No	Yes	NR
		China	2	40	Yes	–	No	Yes	
Carosso A [9]	Eur J Obstet Gynecol Rep Biol	Italy	1	37	–	Yes	No	NO	Negative in placenta, vagina and breastmilk, positive rectal and stool
HU X [10]	Obstet Gynecol	China	1	40	Yes	–	No	No	NR
Alzamora MC [11]	Am J perinatol	Peru	1	33	Yes	–	No	No	NR
Panama Case [12]	The Prensa	Panama	1	37	–	Yes	No	No	NR
Kirtsman [13]	CMAJ	Canada	1	35	Yes		No	No	Positive in placenta, vagina and breastmilk.
Total	10	6	15		11	4	2	7	

Discussion

This review shows that there is perinatal or neonatal infection with SARS-CoV-2 by finding a positive PCR and clinical manifestations of the disease in the first days of birth. In addition, this review shows that there is a possible risk of neonatal infection if the birth is vaginal or if exists premature rupture of the membranes before cesarean section. We cannot rule out vertical transmission according to the route of birth, however, there seems to be less risk with a cesarean section. More cases are necessary to conclude, however it is necessary to bear in mind the results of this review.

The SARS-CoV-2 virus generates mainly pulmonary complications and respiratory specimens are the place where it is found most, however, the second place where its presence has been demonstrated is the gastrointestinal system registered by PCR of the virus in feces [1,2,15]. Even, has been reported in feces [1,16] for a longer time and even after the disappearance of respiratory symptoms.

All this evidence leads to the possibility of finding the virus on a perianal area. The proximity between the anus and the vagina is even less than the proximity between the nose and the mouth. This is the reason why it is necessary to know about the presence of

SARS-CoV-2 at the perianal area and at the vaginal secretions. There are no studies in pregnant women or women of reproductive age that have evaluated this possibility, however, there are some case reports [9,13,17] and case series [18] that have evaluated the presence of the virus at the vaginal secretions and one case (6.25%) was positive [13]. Interestingly, the virus has been found in feces and rectal area [9,18] in two of 10 published cases (20%). With these data, there is a theoretical risk of neonatal infection during natural childbirth due to the close passage of the nose and mouth of the newborn with the anus of the mother, and also that during birth, the professional attending the delivery has contact with the perianal area and the newborn, umbilical cord and placenta. This would lead to more neonatal SARS-CoV-2 infection with vaginal delivery than by cesarean section, however it takes some time for virus incubation and diagnosis, this may explain why the cases are negative, since the sample is taken at birth.

Currently, for every 10 births of mother with COVID-19, nine are by cesarean section, therefore, if there is no transmission associated with the birth route, the expected association between cesarean section and natural delivery with infected newborn would be 9:1 ratio (cesarean section: natural delivery) and

this review shows a ratio of 4:1, being more than double than expected. Therefore, it suggests a possible relationship with the route of birth, however, we must bear in mind that there are few cases currently published.

The herpes virus, human papilloma virus, AIDS and bacteria such as group B streptococcus can be transmitted to the newborn at the time of birth vaginally [19–21], and its prevention has been largely demonstrated with cesarean birth, with the exception that there are already treatments that can be used to treat those infections. This history of infectious diseases and neonatal infection is another valid argument to support a greater possibility of neonatal infection with SARS-CoV-2 at the time of delivery.

One of the cases well described in this review is that of Carroso et al. [9], interestingly, in our hospital there was a similar case. COVID-19 positive woman, arrives in labor, delivery is attended without problems, the newborn is full-term, with Apgar 9/9. The newborn undergoes nasopharyngeal PCR at 24 h and is positive, however, at 72 h it is negative, and its immunoglobulins are negative. Both patients discharged healthy [12]. That case was not published in a medical journal, but it was made public and as it was in our hospital. This case was a motivator for this review.

Another interesting finding of this review is the presence of premature rupture of membranes in two infants with SARS-CoV-2 confirmed by PCR and with clinical manifestation of the disease, both were born by cesarean section [3]. This is also a well-known risk factor for perinatal infection in pregnant women with genital herpes, HIV and streptococcus [19–21]. Another interesting point to analyze is the use of corticosteroids in those patients with premature rupture of membranes. Currently, the analyzes suggest us to use corticosteroids in patients with COVID-19 and premature rupture of membranes far from term [22].

Of course, with the cases found in this review we cannot rule out contagion on contact with the mother, despite the fact that were separated from their mothers and breastfeeding was not allowed. Failure to perform analysis at the perianal, vaginal, umbilical cord, placental, amniotic fluid and possible contact with the mother leaves doubts. However, a single negative PCR test in these specimens and also in all newborns of a COVID-19 positive mother also raises questions. With regard to vaginal delivery, it is possible, having the virus at the perianal area and contamination occurs, that the test is negative in the newborn if performed at birth; therefore, if the PCR is negative after birth, we consider it appropriate that

this test be repeated between 2 and 5 days after birth [3], for the possible incubation period.

With a vaginal delivery in pregnant with positive COVID-19, there are several moments in which the newborn can become infected: Into the uterus *via* the placenta, during the birth by direct contact with an infected perianal area, by contact of the health professional who has had contact with the infected perianal area, by aerosols existing in the area generated by the mother since it is about 1 m away making effort with the discomfort of the mask, by direct contacts with the mother, for not giving adequate isolation of mother/child and for breastfeeding.

This extensive review finds 15 cases of newborns positive for SARS-CoV-2 according to the PCR examination carried out just at birth, hours after or in the first days of birth; in seven there are clinical and radiological findings of the disease and also these newborns did not have contact with the mother from birth. The positive PCR finding in the 15 neonates and no contact with their mother demonstrate the existence of the disease at birth or developed in the first hours or days after birth, and the clinical manifestation in 7 newborn confirms the neonatal infection acquired through the mother before birth, during natural delivery or during cesarean section.

In summary, this review shows that exist perinatal COVID-19 infection linked at birth and with greater possibility if the birth is natural, so it would be appropriate to perform a perianal PCR before delivery. Vaginal delivery and premature rupture of membranes should be considered as risk factors for perinatal infection; however, studies are urgent to confirm or rule out this association.

Contributions of authorship

Author's contribution: PV-D conceived the study. PV-D, REM and CL contributed to its design, PV-D, REM and CL search, review and analyze the papers, PV-D, REM and CL interpret results. PV-D, REM and CL revised the manuscript. All authors approved the final manuscript as submitted.

The corresponding author and who takes responsibility for the integrity of the data and the accuracy of the data analysis is Paulino Vigil-De Gracia.

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