

## Review Article

# Vertical Transmission of Covid-19-A Systematic Review

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### Abstract:

**Aim:** Recently, the first case report of a possible vertical transmission of Covid19 infection was published on the *Journal of American Medical Academy*, while previous reports showed absence of transplacental transmission. Data on a key element of neonatal care in this pandemic, such as the possibility of vertical transmission, are rare.

**Methods:** A systematic literature review was carried out to identify papers on COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the Medline and EMBASE databases between 1 January and 31 March 2020.

**Results:** A total of 70 newborns, born to mothers with proved Sars-Cov-2 infection, from nine different studies were cumulatively analyzed in our research. A total of sixty-five neonates (92.9% of cases) from seven independent studies was negative for a transplacental

infection according to oropharyngeal or nasopharyngeal swab performed in the first hours or days of life; four patients (5.7% of cases) had early infection detected at second days of life, and vertical transmission could not be excluded; finally, one patient had a negative throat swab but positive IgM and IgG count, and was considered possibly infected in utero. Cumulatively, in 5 out of 70 cases (7.1% of neonates), a vertical transmission could not be excluded or was considered possible.

**Conclusions:** Findings suggesting a possible vertical transmission of Covid-19 are increasingly reported. Transplacental transmission of the infection cannot be excluded.

**Keywords:** Covid-19; Vertical transmission; Transplacental transmission

## **1. Introduction**

On March, 26th 2020 a first case report of possible vertical transmission of Covid-19 infection was published on the Journal of American Medical Association [1]. The paper reports the case of a neonate born to a mother with COVID-19 who had elevated antibody levels and abnormal cytokine test results 2 hours after birth. The elevated IgM antibody level suggests that the neonate was infected in utero. Since the IgM antibodies are not transferred to the fetus via the placenta, this finding lead to hypothesize a possible transplacental transmission of the infection. On the other hand, before this case report was published, all the few studies published reported the absence of vertical transmission [2-4]. National and international scientific societies reacted accordingly [5-6]. The possibility of a vertical transmission of the infection would have huge clinical and scientific implications. A first comprehensive analysis of the available literature about the subject was carried out by Schwartz [7]. Our aim was to lead a new analysis, updated to March 31st, 2020, in view of the recent relevant developments, with a particular focus on the different techniques that were used to identify the possible vertical transmission of the

infection. Secondly, we aimed to discuss possible scientific reasons for this apparently contrasting evidence. Our aim in this paper is to summarize the findings of a systematic literature review on the current knowledge of vertical transmission of COVID-19.

## **2. Methods**

The Medline (used by PubMed) and EMBASE databases were searched for relevant terms related to COVID-19 and SARS-CoV2 in newborn. There were 27 papers published in Medline between 1 January and 30 March 2020 and 4 publications in EMBASE during the same period. Of those, 9 were deemed relevant to this review.

## **3. Results**

In our analysis, nine papers [1-4, 8-12] reported original data about delivery to mothers infected by Sars-Cov-2, involving a total of 70 neonates born to mothers with proved Sars-Cov-2 infection. Authors, study design, sample size, method used to assess maternal-fetal transmission, delivery method and neonatal prognosis are reported in Table 1.

Authors	Study design	Sample size	Gestational age	Delivery method	Tests to assess mother-to-child transmission	Tests results	Newborn prognosis
<i>Chen W. et al.</i> [2]	Retrospective	9 (only 6 neonates tested)	36W or above	C-section	amniotic fluid, cord blood, neonatal throat swab, breastmilk samples qRT-PCR	100% negative	Unavailable information
<i>Zhang et al.</i> [9]	Retrospective	16 (only 10 neonates tested)	35+5W or above	C-section	Neonatal oropharyngeal swab qRT-PCR	100% negative	Unavailable information
<i>Wang et al.</i> [10]	Case report	1	40W	C-section	amniotic fluid, cord blood, neonatal throat swab, breastmilk samples qRT-PCR	Throat swab <b>positive</b> (36h of age). All other samples negative	Discharged
<i>Liu et al.</i> [4]	Case series	3	38W or above	66% C-section (N=2) 33% vaginal (N=1)	Neonatal oropharyngeal swab, blood, cord blood, urine and feces qRT-PCR	100% negative	Discharged
<i>Zhu et al.</i> [3]	Retrospective	10	40% full-term infants 60% premature infants	78% C-section (N=7) 22% vaginal (N=2)	Neonatal oropharyngeal swab	100% negative	50% discharged (N=5) 40% hospitalized (N=4) 10% death (N=1)

<i>Zeng et al.</i> [11]	Cohort study	33	12% premature infants 88% full-term	78% C-section (N=26) 22% vaginal (N=7)	Neonate oropharyngeal and anal swab qRT-PCR at 2, 4 and 6 days of life	91% negative (N=30) 9% positive (N=3)	Stable vital signs or discharged
<i>Wang X et al</i> [12]	Case report	1	30W	C-section	Neonatal oropharyngeal swab and stools, amniotic fluid, cord blood, placenta qRT-PCR	Negative	Discharged
<i>Dong et al.</i> [1]	Case report	1	34+2W	C-section	Nasopharyngeal swab, maternal vaginal secretions and breastmilk RT-PCR; specific maternal and neonatal IgG and IgM	Positive IgG and IgM count Negative nasopharyngeal swab and vaginal secretions	Hospitalized
<i>Chen S et al.</i> [13]	Retrospective	5	Full term	60% vaginal (N=3) 40% C-section (N=2)	Neonate throat swab qRT-PCR	100% Negative	Discharged

**Table 1:** Characteristics of the analyzed studies.

Four retrospective studies, three case reports, one case series and one cohort study were present. Sample size ranged from 1 to 33 patients. Full-term deliveries were the majority, but five papers reported preterm deliveries [1, 3, 9, 11, 12]. Cesarean section was the preferred delivery method, used in 81% of cases (57 out of 70), while vaginal deliveries were reported in 19% of cases (13 out of 70). In particular, four studies reported vaginal deliveries in Sars-Cov-2-infected women [3, 4, 11, 13]. None of the neonate born by natural delivery had a positive test for Covid-19 infection. All the deliveries were carried out in accordance with the international expert consensus in terms of prevention of infection transmission [14], namely: delivery in a negative-pressure isolation room when available, the mother wore an N95 mask and did not hold the infant. This makes the possibility of intra-partum transmission reasonably unlikely.

A total of 70 newborn were cumulatively analyzed in our study. A total of sixty-five newborns (92.9% of cases) from seven independent studies [2-4, 9, 11-13] was negative for a transplacental infection according to oropharyngeal or nasopharyngeal swab performed in the first hours or days of life; four patients (5.7% of cases) from two different studies [10, 11] reported early-onset infection detected at second days of life, for which vertical transmission could not be excluded; finally, one patient, as reported in the paper by Dong et al. had a negative throat swab but positive IgM and IgG count, and was considered possibly infected in utero. Cumulatively, in 5 cases (7.1% of neonates), a vertical transmission could not be excluded or was considered possible.

Six studies, with different methods of investigation, reported the absence of vertical transmission of Sars-Cov-2 [1-4, 8, 9]. In three other studies [10-12], in view of early-onset infections in the newborn a vertical

transmission of the infection was defined as “impossible to exclude” or “possible”. All neonates were tested with qRT-PCR techniques on oropharyngeal or nasopharyngeal swab samples. Additional tests to further investigate the possibility of mother-to-child transmission were performed in some cases. In particular, amniotic fluid was examined using RT-PCR in two different studies [2, 12] (a total of 7 cases) and resulted negative in both. Cord blood was examined in four studies (eleven cases in total) [2, 4, 10, 12] and the presence of Sars-Cov2 infection was ruled out in all. Breastmilk was analyzed in three different studies [1, 2, 10], with a total of 8 cases, and none proved the presence of the virus in the milk. Placenta specimen resulted negative to Covid-19 in two different case-reports [10, 12]. Vaginal secretions, that may have a role in intrapartum transmission of the disease, were negative in the paper by Dong et al. [1]. Other analyzed specimen included: urine, feces, anal swab, and serum plasma. The study by Dong et al. was the only one to evaluate specific antibody titer, showing increased specific IgM and IgG in a neonate at two hours of life.

#### 4. Discussion

Since the beginning of the Covid-19 pandemic, the possibility of mother-to-child transmission has been the subject of intense research activity. Experiences and knowledge derived from previous respiratory viruses epidemic were the starting point for the first investigational activities [15]. The majority of the Authors, beginning from the paper by Chen et al. published on *The Lancet* [2], reported the absence of infection in neonates born to mothers with Covid-19. Different organic specimen, such as amniotic fluid, cord blood, breastmilk and obviously throat swab were analyzed and resulted negative to Sars-Cov-2. Other studies reported concordant findings [3, 4, 9]. On the other hand, the study by Dong et al. reports the case of a neonate (born to a mother with COVID-19) who had

elevated antibody levels and abnormal cytokine test results 2 hours after birth. The elevated IgM antibody level suggests that the neonate was infected in utero, since IgM antibodies are not transferred to the fetus via the placenta. The hypothesis of a possible transplacental transmission in this case is based on a strong scientific rationale: the well-known mechanisms of permeability of the placental barrier to different classes of antibodies and the use of IgM as markers of recent immune response to a specific pathogen.

The paper by Dong et al. is not the only one to demonstrate a possible vertical transmission of the disease. A particular case is represented by the report from Wang et al. [10]. The authors reported a neonate, born to an infected mother, was tested positive (with oropharyngeal swab) at 36 hours of age. In this case, vertical transmission could not be ruled out. Similarly, three neonates in the study by Zeng et al. [11] had a positive nasopharyngeal swab in their second day of life. In these four cases of early onset infection, transplacental transmission could not be excluded and, as stated by the authors, some elements are consistent with a possible vertical transmission. In particular, prophylactic measures to avoid mother-to-child transmission in order to avoid intra and post-partum transmission were respected, other at-risk contacts were absent, and the onset of the infection preceded the usual minimum incubation time.

A key element to understand currently available evidence is to focus on the methods used to determine mother-to-child transmission of the disease. A pharyngeal swab in the first days or even hours of life was used in all the studies we analyzed. Complemental exams, such as RT-PCR on amniotic fluid, placental specimen, cord blood and other specimen were performed in some cases. The study by Dong et al. was the only one to evaluate the antibody response of a

neonate born to a mother with Covid-19. Interestingly, in their study, while the increase of IgG and IgM proved a possible vertical transmission of the disease, pharyngeal swab resulted negative for Sars-Cov-2. This finding is in accordance with the study by Chen et al. [2] and with the other papers included in this review. Remarkably, little is known about viral replication and inflammatory response to Sars-Cov-2 in the neonate. Age-specific pattern of immune reaction and other physiological factors may influence the response to Sars-Cov-2 in the neonatal sub-population [16]. In this situation of uncertainty, the study of antibody response to Covid-19 in the newborn may be a useful tool to scientifically investigate possible mechanisms of in utero transmission.

## 5. Limits

The main limit of our research was that the amount of data on this specific topic is still scarce. Secondly, in view of the limited available data, studies conducted with different designs and case reports were included in the review. Furthermore, only one perspective cohort study was available, while most of the findings came from retrospective research. Finally, the nature of the review is clearly time-sensitive and hopefully many future studies will contribute to the research process in the next future,

## 6. Conclusions

According to our review, it is not correct to state that the possibility of vertical transmission of Covid-19 has been definitely confirmed nor excluded. On the other hand, cases of possible transplacental transmission of the infection are increasingly reported, and in view of the small amount of data currently available, this possibility cannot be ruled out. Further studies, on a larger scale, possibly focusing on the evaluation of specific antibody response in the newborn, are urgently needed.

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