

# Congenital and Intrapartum SARS-CoV-2 Infection in Neonates: Hypotheses, Evidence and Perspectives

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## ABSTRACT

**INTRODUCTION** Both intrauterine and intrapartum mother-to-child transmission of SARS-CoV-2 have been reported. However, there is still disagreement as to the likelihood and frequency of such vertical transmission.

**OBJECTIVE** Summarize and analyze the published evidence on forms of SARS-CoV-2 vertical transmission (either intrauterine or intrapartum).

**EVIDENCE ACQUISITION** We carried out a review of literature published in English and Spanish from January 1, 2020 through October 30, 2020. Search engines included PubMed/MEDLINE, SciELO, LILACS, Cochrane, Google Scholar, ResearchGate and medRxiv. There were no restrictions concerning type of study. The review included 48 original research articles, 11 review articles, a meta-analysis, 2 pre-published articles, 15 systematic reviews, and 10 editorials or comments.

**DEVELOPMENT** Medical thinking on congenital or intrapartum maternal-fetal/neonatal transmission of SARS-CoV-2 has evolved from preliminary evidence that was divided as to whether these forms of vertical transmission were even possible to current evidence support-

ing both forms of transmission and hypothesizing as to the mechanisms that guide them. The presence of the SARS-CoV-2 virus in maternal, placental, fetal or neonatal tissues has been demonstrated by RT-PCR, specific immunoglobulin detection tests, immunostaining and in-situ hybridization. It is estimated that infections acquired either congenitally or intrapartum occur in 1.8%–8.0% of newborns born to women who test positive for COVID-19 at the end of their pregnancies. This review found 53 neonates who were diagnosed with COVID-19 in the first 48 hours of life by either RT-PCR or specific IgM tests. According to criteria outlined in this review, the timing of infection corresponded to congenital or intrapartum transmission in 39.6% (21/53) of COVID-19–positive newborns, to postpartum transmission in 15.1% (8/53) and remains unspecified in 45.3% (24/53).

**CONCLUSIONS** Congenital and intrapartum SARS-CoV-2 infection in the fetus/newborn is possible, but rare. International collaborative studies using common epidemiological surveillance instruments would allow for a more precise specification of the frequency of congenital and intrapartum SARS-CoV-2 infection at the population level.

**KEYWORDS** COVID-19; SARS-CoV-2; vertical transmission of infectious disease; infant, newborn

## INTRODUCTION

Since the outbreak of the novel coronavirus in late 2019, there have been indications of SARS-CoV-2 infections in neonates.[1] Such infection can be due either to 'vertical' transmission (from mother to child) or to 'horizontal' transmission (from familial contacts or nosocomial infections acquired during hospitalization).

Vertical transmission can occur by one of three mechanisms: intrauterine infection (transplacental or ascending), intrapartum infection (transmission that occurs during birth) and postpartum infection (through breast milk, nasal secretions, etc.) Evidence of transplacental transmission of emerging diseases like HIV, Ebola and Zika suggest the possibility of intrauterine or intra-amniotic transmission of SARS-CoV-2 infection.[3] Positive results from quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA during the first few hours or days of life and identification of newborns with manifestations of early-onset clinical signs and symptoms of COVID-19 would confirm vertical SARS-CoV-2 infection.[1,3]

Given that postnatal transmission from mother to child is also considered 'vertical transmission', the term is imprecise, prompting increasing use of the categories proposed by Shah.[4] Under this

definition, 'vertical transmission' includes congenital infections with intrauterine or perinatal fetal death, congenital infections in living newborns, neonatal infections acquired intrapartum and neonatal infections acquired postpartum (Figure 1).

Determining the possibility of maternal SARS-CoV-2 infection during pregnancy has obvious implications for clinical practice and healthcare. Among others, these include: 1) giving parents a better understanding of the probability of vertical transmission and how it could affect their current or future offspring; 2) allowing for compliance by obstetricians and neonatologists with measures suggested by perinatal care protocols designed to minimize the risk of vertical transmission (e.g. transmission related to the birth route, immediate isolation of suspected or study cases) and guidelines for early maternal skin-to-skin contact, newborn care, optimal time for cord clamping, etc;[5] and 3) allowing for implementation and development of specific protection measures for healthcare workers to help prevent infection during delivery, patient care and neonatal resuscitation. It would also allow the scientific community to evaluate treatments and design drugs aimed at minimizing the risk of transplacental or intrapartum transmission.

Even when both intrauterine and intrapartum mother-to-child transmission of SARS-CoV-2 have been reported, there is still disagreement as to their likelihood and frequency. This article presents a review of current available knowledge on congenital and intrapartum transmission of SARS-CoV-2.

## EVIDENCE ACQUISITION

We reviewed literature published on the topic of SARS-CoV-2 vertical transmission through an exhaustive search of the

## IMPORTANCE

This article summarizes evidence available on congenital and intrapartum SARS-CoV-2 infection, an understudied aspect of the COVID-19 pandemic that requires more study due to its clinical and healthcare implications.

Pubmed/MEDLINE, SciELO, LILACS, Cochrane, Google Scholar, Research Gate and medRxiv databases. There were no restrictions on study type. We used the following search terms: COVID-19, SARS-CoV-2, intrauterine infection, neonatal infection, vertical transmission; as well as their Spanish equivalents. We also searched through the references of review papers that emerged during the search for all other relevant sources. When several reports documented the same case, a single report was selected.

The quality of reports and case series were evaluated using an instrument developed by the Mayo Clinic Center for Evidence-Based Practice.[6] Descriptive observational studies were evaluated using a modified version of the Newcastle-Ottawa scale first introduced by Kotlyar.[7] Evaluation of single studies and document classification was performed independently by each of the authors, who then cross-compared their criteria and resolved their discrepancies as a team. After a thorough selection of the reviewed literature using the above criteria, our review contained 87 publications: 48 original articles, 11 review articles, 1 meta-analysis, 2 pre-publication articles (articles that have not yet undergone peer review), 15 systematic reviews, and 10 editorials or comments.

Only cases documenting congenital infection in live newborns or suspected intrapartum infection were selected, and only if the mother had been diagnosed with COVID-19 during her third trimester of pregnancy and the RT-PCR or serological antibody tests for immunoglobulin M (IgM) were positive in the newborn in their first 48 hours of life. In symptomatic neonates, the clinical manifestations should also have occurred within the first 48 hours.

We classified infections according to criteria established by Shah (Figure 1),[4] which specify detection of SARS-CoV-2 in chorionic villi through electron microscopy, through immunohistological techniques using antibodies against viral antigens, and in situ hybridization (detection of RNA targets without affecting cell morphology).[3,8,9]

Patients whose clinical manifestations occurred  $\geq 48$  hours after birth were classified as postnatally-acquired neonatal infections. This is in line with Shah's criteria.[4] If it was not possible to specify when the initial infection occurred, the case was classified as 'not yet specified'. We classified maternal infection severity according to guidelines proposed by Wu and McGoogan:[10] mild (without pneumonia or with mild pneumonia); severe (dyspnea, respiratory rate  $\geq 30$  respirations per minute, oxygen saturation  $\leq 93\%$ , ratio of partial pressure of oxygen to inspired fraction of oxygen  $< 300$  and/or pulmonary infiltrates  $> 50\%$  in 24–48 hours); or as critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[10]

## DEVELOPMENT

**Diagnosis of congenital and intrapartum SARS-CoV-2 infection** Evidence of viral replication in fetal lung tissue would provide the most conclusive evidence for intrauterine transmission, but this evidence is inaccessible for obvious technical and ethical reasons. It has therefore been proposed that clinical evidence of vertical transmission be obtained by isolating the virus from samples taken from the placenta, amniotic fluid, umbilical cord

and pharyngeal swabs immediately after birth. This last criterion is the one used in clinical practice when testing for intrauterine transmission of SARS-CoV-2.[11]

Among newborns of COVID-19–positive mothers who have also tested positive for SARS-CoV-2, there are asymptomatic cases and cases in which the disease appeared anytime in the first few hours or the first days after birth. Given our current lack of knowledge on infection mechanisms and timing, early-onset disease has been presumed by some authors to be the result of vertical transmission. This practice is under discussion. There is no current consensus defining early-onset neonatal COVID-19; and in fact, time limits vary among studies even for neonatal bacterial infections.[8,12]

The classification scheme proposed by Shah[4] attempts to resolve these inconsistencies based on the direction in which disease transmission occurred by including precise indicators of the most frequently used diagnostic methods for detecting the virus. As there is very little knowledge about SARS-CoV-2 incubation periods in the fetus or neonate, the time periods proposed for each category of infection could change as the incubation process becomes better understood. Symptoms present from birth up to 48 hours after birth indicate congenital or intrapartum infection, but do not confirm whether the infection was transplacental, and the presence of SARS-CoV-2 in placental tissue demonstrated by RT-PCR is not necessarily an indication of transplacental transmission. The efficacy of RT-PCR analysis of nasopharyngeal swab samples in newborns in diagnosing congenital or intrapartum infection has not yet been demonstrated. [8,13,14] The classification scheme by Shah[4] makes reference to specific clinical manifestations of SARS-CoV-2 infection, but the clinical presentation of COVID-19 in newborns is still poorly understood, and both clinical markers and imaging findings remain nonspecific.

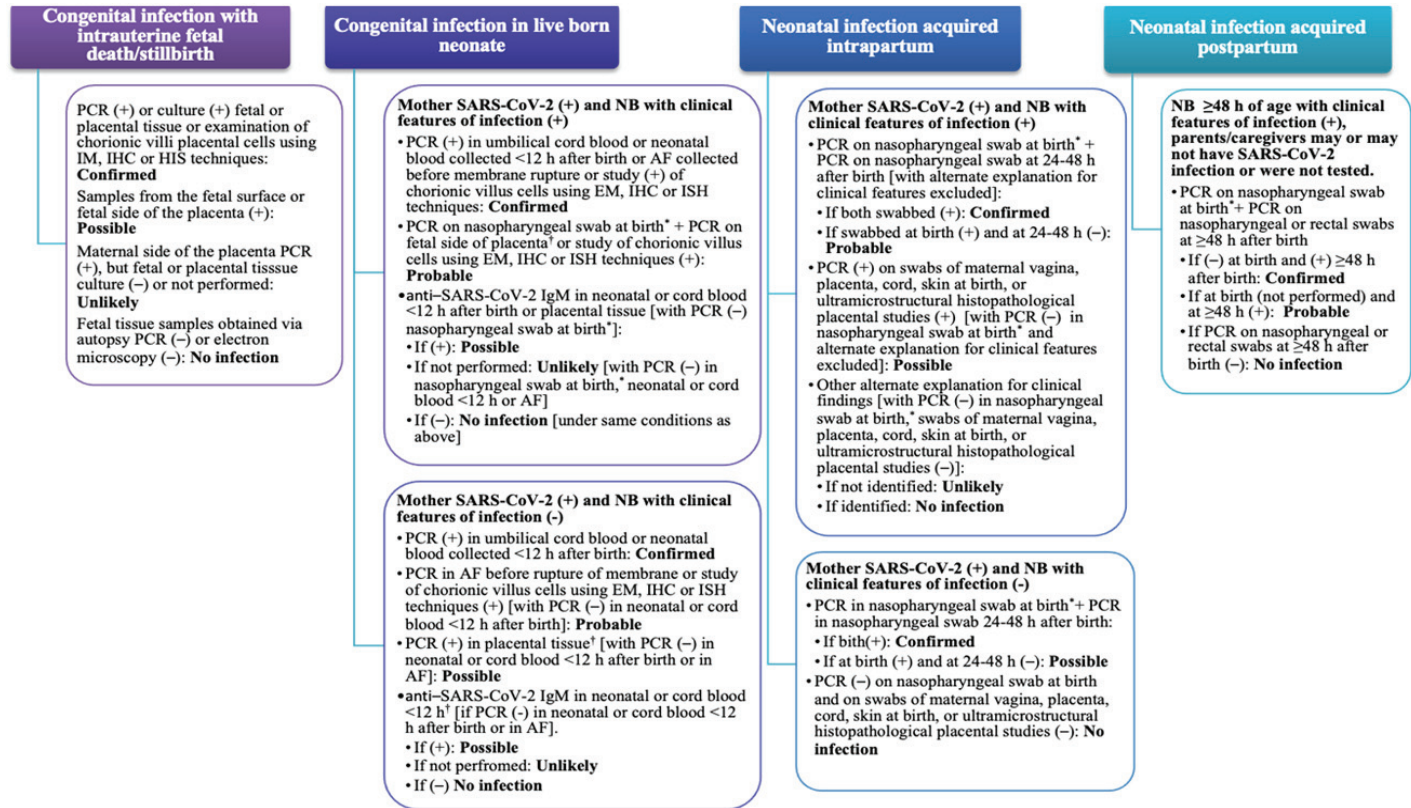
We present the current state of medical thinking on maternal–fetal/neonatal transmission of SARS-CoV-2, based on studies conducted in newborns of mothers diagnosed with COVID-19 in the third trimester of pregnancy. The information is classified into three groups: evidence that supports non-transmission, evidence of early neonatal infection without demonstrated vertical transmission, and evidence that supports congenital or intrapartum transmission with differing degrees of certainty. The evidence supporting congenital or intrapartum infection was classified according to three out of the five case categories proposed by Shah:[4] confirmed (strong evidence of infection with confirmatory microbiology), probable (strong evidence of infection but lacking confirmatory microbiology) and possible (evidence suggestive of infection but inconclusive).

### Group one: no evidence of SARS-CoV-2 vertical transmission

The hypothesis that the SARS-CoV-2 virus is not transmissible to the fetus or newborn via transplacental or intrapartum routes is based on the fact that no cases of vertical transmission were documented during previous coronavirus epidemics (SARS-CoV-2 in 2002 and MERS-CoV in 2014) or in either disease since. [15]

In most studies carried out early in the COVID-19 pandemic on whether congenital or intrapartum transmission was possible from infected women, presence of the virus could not be demonstrated

Figure 1: Fetal/neonatal SARS-CoV-2 infection



\*after cleaning the newborn, †born via cesarean section before rupture of membrane, NB: newborn, AF: amniotic fluid, (+): positive, (-): negative, EM: electron microscopy, IHC: immunohistochemistry, ISH: in-situ hybridization.  
 Category definitions: Confirmed, Strong evidence of infection with confirmatory microbiology; Probable, Strong evidence of infection but confirmatory microbiology lacking; Possible, Evidence suggestive of infection but incomplete; Unlikely, Little support for diagnosis but infection cannot be ruled out; Not infected, No evidence of infection.  
 Prepared by Shah[4] (modified by the authors).

in either vaginal secretions, amniotic fluid, tissue samples from the placenta or umbilical cords, or neonatal pharyngeal swabs. [1,11,16,17]

Penfield[18] demonstrated exposure to SARS-CoV-2 in three neonates of mothers with severe or critical COVID-19 whose placental or ovular membrane samples were positive for SARS-CoV-2. However, none of the neonate samples were positive and none of the newborns showed symptoms of the disease, so the work in question could not demonstrate maternal-fetal transmission.

In this context, it should be noted that little attention has been paid to the proportion of false negatives in RT-PCR tests in children of COVID-19-positive mothers, which, according to studies performed on other age groups, can be up to 100% when sampling is performed the first day of the incubation period of the disease and 67% if performed on the fourth day.[19] Thus, it is entirely possible that cases reported as negative at birth or in the first few hours after birth are false negatives.

**Group two: early neonatal SARS-CoV-2 infection without demonstrated vertical transmission** The possibility of transmission during childbirth was considered when the first cases of newborns with COVID-19-positive mothers tested positive by RT-PCR. Wang[20] reported a newborn who presented with a positive nasopharyngeal sample 36 hours after birth whose COVID-19-positive mother tested negative (by RT-PCR) in samples taken from the pla-

centa, umbilical cord and breast milk (Table 1). For similar reasons, it was not possible to prove intrapartum or congenital infection in case series published in China documenting positive pharyngeal samples taken 24–36 hours after birth.[21–23]

Two neonates of mothers with severe or critical COVID-19 tested positive for SARS-CoV-2, one of them in Peru and one in Great Britain, with nasopharyngeal samples obtained, respectively, at 16 hours of life and at birth.[24,25] A newborn tested positive in Italy one day after birth, after receiving breastmilk from their mother, who was unaware that she was positive for COVID-19. [26] The absence of evidence of SARS-CoV-2 in amniotic fluid, umbilical cord blood or placenta makes it impossible to confirm that any of these cases arose from a congenital or intrapartum infection; nor was it possible to determine the timing of infection in four other positive newborns according to RT-PCR in respiratory samples after birth, one reported by Kalane[27] and three others by Savasi.[28]

A prospective population cohort study in Great Britain found 12 SARS-CoV-2-positive infants born to mothers with COVID-19, 6 of whom had samples obtained in the first 12 hours of life.[29] This raises the possibility that these infections were acquired either congenitally or during birth, but this cannot be confirmed due to the lack of evidence that would pinpoint the timing of infection. This means these infections must be classified as ‘undetermined’ as to the timing and route of infection.[29] The same is true for six neonates reported by Sola,[30] all of whom had positive nasopharyngeal samples obtained

16–36 hours after birth; this study involved 86 pregnant women with COVID-19 confirmed by RT-PCR in seven countries (6 from Latin America, and Equatorial Guinea).

**Group three: SARS-CoV-2 congenital or intrapartum transmission confirmed (strong evidence of infection with confirmatory microbiology), probable (strong evidence of infection but confirmatory microbiology lacking) or possible (evidence suggestive of infection but incomplete).** The third category summarizes information on SARS-CoV-2–positive newborns for whom we know the timing of infection, who were diagnosed in the first 48 hours of life, and who were born to mothers who contracted COVID-19 in their third trimester (Table 2). Vivanti[31] offered the strongest evidence of transplacental transmission of SARS-CoV-2; namely a preterm newborn who presented with depression at birth followed by neurological signs. RT-PCR tests on the placenta and amniotic fluid were positive for SARS-CoV-2, and immunohistochemical examination of the placenta detected viral nuclear proteins. RT-PCR performed on samples from neonatal lavage, blood, nasopharynx and rectum were also positive. Only cerebrospinal fluid was negative. This case has been classified as a confirmed congenital infection of SARS-CoV-2, with associated neurological manifestations.

There are three other cases of SARS-CoV-2–positive newborns with confirmed congenital infections. The first was a symptomatic full-term newborn whose RT-PCR on respiratory samples was deemed ‘doubtful’ at birth and positive at 36 and 72 hours of life. Presence of SARS-CoV-2 was also confirmed by electron microscopy, immunohistochemistry, and in situ hybridization.[32,33] The second case was a symptomatic neonate born to a symptomatic mother whose nasopharyngeal samples were negative for SARS-CoV-2 but whose serological studies were positive for the virus. RT-PCR tests taken from the newborn’s nasopharynx, from the placenta and from umbilical cord blood were all positive at birth.[34] The third case involved an asymptomatic neonate with negative RT-PCR tests on nasopharyngeal samples on the first and third days of life who nevertheless had positive molecular studies of cord blood and placenta.[35]

Some of the first evidence of congenital SARS-CoV-2 infection was provided by Zamaniyan, who isolated the virus in amniotic fluid using RT-PCR.[36] Nasopharyngeal samples were positive at 24 hours and 1 week of life, but samples from umbilical cord blood, the nasal cavity and the pharynx were negative at birth, making congenital infection likely, given the presence of the virus in the amniotic fluid. Kirstman demonstrated SARS-CoV-2 presence on both the maternal and fetal sides of the placenta in a neonate whose nasopharyngeal samples were positive at birth.[37]

Patanè found RT-PCR evidence of SARS-CoV-2 infection in the mother, the placenta and the newborn.[38] Patanè’s study included 22 mother–child dyads, in which only two neonates tested positive for SARS-CoV-2. The first newborn had positive nasopharyngeal samples at birth, at 24 hours and at 7 days after birth; and the second was negative at birth but positive at 7 days of life, despite having no contact with the COVID-19–positive mother during this time. Presence of messenger RNA from SARS-CoV-2 spike proteins at the syncytiotrophoblast level was confirmed via in situ hybridization. Both of these cases were classified as probable congenital infections. However, given that nasopharyngeal samples in the second newborn were only positive after seven days of life, this case pushes the boundaries

of what we can consider a congenitally-acquired infection and raises the question of whether a positive nasopharyngeal sample obtained after 48 hours accompanied by viral detection on the fetal side of the placenta via in situ hybridization counts according to the classifications used in this review.[4] Both newborns presented with slight feeding difficulties.

Another neonate reported by Sisman[9] was classified as ‘probable’ for congenitally-acquired COVID-19, while a newborn in a study published by Carosso[39] was classified as ‘possible’ for infection acquired intrapartum.

Specific tests for IgG and IgM antibodies against SARS-CoV-2 have suggested the possibility of vertical intrauterine transmission in at least three studies.[40–42] In the first two studies,[40,41] three neonates had elevated levels of SARS-CoV-2–specific IgM and IgG. However, negative RT-PCR tests coupled with rapidly declining levels of SARS-CoV-2–specific antibodies in neonatal serum cast doubt on whether these antibodies were produced in the fetuses or neonates or were, instead, relics from the mothers.[43] Unlike IgG antibodies, IgM antibodies do not usually cross the placental barrier. As they can be produced by the fetus, their presence in neonatal serum has been used in diagnosing congenital infections, although the high proportion of false positives and false negatives (likely due to cross-reactivity) has limited their usefulness as diagnostic tests.[8,43,44]

Gao[42] reported on an asymptomatic neonate born to a mother with confirmed symptomatic COVID-19 at 33 weeks gestation. On the day of delivery, both mother and child had negative RT-PCR results from pharyngeal, placental and amniotic fluid samples, but levels were high for IgG and IgM specific to SARS-CoV-2. The possibility of acute maternal and neonatal postpartum infection was ruled out as serial RT-PCR tests performed on the newborn up to 14 days after birth were all negative, with only one positive single-step reverse-transcriptase droplet digital PCR (RT-ddPCR) test—RT-ddPCR is more sensitive than RT-PCR—on the seventh day of life, and the levels of antibodies steadily decreased. Histological studies showed inflammation in the placenta. According to the criteria proposed by Shah,[4] these last four cases of newborns could be classified as congenitally-acquired SARS-CoV-2 infections.

It was difficult to distinguish whether the case reported in Mexico by Hinojasa-Velasco[45] was acquired congenitally or intrapartum, as no samples from the umbilical cord, neonatal blood, placenta or nasopharynx were tested during the time period specified by the criteria outlined in this study.[4] Postpartum infection was ruled out.

Three neonates reported in the series by Martínez-Pérez[46] and two reported by Schwartz[47] were classified as infections possibly acquired intrapartum, as they could not be confirmed as the positive RT-PCR tests on samples from the nasopharynx taken at birth were not repeated 24–48 hours later. McDevitt [48] described a case of possible intrapartum infection garnered from an observational study of neonates included in a universal screening. The neonate in question had positive RT-PCR results at nine hours after birth. The mother was also positive. Both mother and baby were asymptomatic.[48]

The literature we reviewed includes other cases of probable postpartum SARS-CoV-2 infection diagnosed at 48 hours of life

**Table 1: Neonates of COVID-19–positive mothers who tested positive for SARS-CoV-2 in the first 48 hours of life, for whom the timing of infection cannot be pinpointed**

Reference	Wang [20]	Nie [21]	Khan [22]	Khan [22]	Zhang [23]	Alzamora [24]	Govind [25]	Ferrazzi [26]	Kalane [27]	Savasi [28]	Knight [29]	Sola [30]
Country	China	China	China	China	China	Peru	Great Britain	Italy	India	Italy	Great Britain	Latin America and Equatorial Guinea
Study type	CR	DO	CS	CS	CS	CR	CS	DO	CR	DO	DO	DO
Evidence quality	Good	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Good	Poor	Fair	Fair
Mothers (No.)	1	1	1*	2*	1	1	1	1	1	3**	6**	6**
Maternal symptoms	S–M	S–M	S–M	A	S–M	S–SC	S–SC	S–U	S–M	S–M	S–NS	S–NS
GA (weeks)	40	NS	40	39	39	33	39	NS	32	NS	PT 3, FT 3	NS
Birth type	C	C	C	C	C	C	C	C	C	V	C	NS
RT-PCR, NP/OP	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
RT-PCR, vaginal secretions	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	No	NS
RT-PCR, breast milk	(–)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Newborns (No.)	1	1	1*	2*	1	1	1	1	1	3**	6**	6**
Apgar 1/5/10 min	8/9	8–9/9–10	9/10	9/10	NS	6/8	5/9	5 min >7	7/7	NS	NS	NS
Neonate symptoms	S	A	A	A	S	S	S	NS	S	A	NS	S
RT-PCR, cord/cord blood	(–)	(–)	(–)	(–)	NS	NS	NS	NS	No	NS	No	NS
RT-PCR, NP/OP	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	ET Secr (+)	(+)	(+)	(+)
Birth- 1 <sup>st</sup> sample (+) (h)	36	36	24	24	30	16	At birth	24	24	24	< 12	16–36
RT-PCR, rectal/stool	(–)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
RT-PCR over time (hours or days)	NP (–) 17 d	OP (–) 4, 8 y 15 d	NS	NS	NS	NP (+) 2 d	NS	NS	ET Secr (+) 4d	NS	NS	NS
RT-PCR, AF	(–)		No	No	NS	NS	NS	NS	No	NS	NS	NS
RT-PCR, placenta, membranes	(–)	(–)	No	No	NS	NS	NS	NS	No	NS	No	NS
Evidence of SARS-CoV-2 in placenta (specific technique)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SARS-CoV-2 IgG/IgM at birth	NS	NS	NS	NS	No	(–)/(–)	NS	NS	NS	NS	NS	NS
Classification	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

CR: case report CS: case series DO: descriptive/observational S-SC: symptoms-severe or critical S-M: symptoms-mild S-NS: symptoms-severity not specified GA: gestational age PT: preterm FT: full-term C: cesarean V: vaginal (+): positive (–): negative NS: not specified RT-PCR: real-time polymerase chain reaction S: symptomatic A: asymptomatic NP: nasopharyngeal OP: oropharyngeal ET Secr: endotracheal secretion IgG: immunoglobulin G IgM: immunoglobulin M IP: intrapartum PP: postpartum \*Different mothers or newborns reported from a same study \*\*Number of mothers or newborns.

by nasopharyngeal RT-PCR or by bronchoalveolar aspirate in children of pregnant women positive for COVID-19 (Table 2).[49–54] During the course of this review, we did not find any case–control or cohort studies that reported the presence of congenital and intrapartum infections as the most likely case.

**Population studies, systematic reviews and meta-analyses** Low incidence of neonatal infection has been found in population studies of COVID-19–positive mothers (confirmed by RT-PCR tests). A prospective cohort study by Khoury in the United States found a 2.5% (6/236) incidence rate of early-onset neonatal infection in newborns of COVID-19–positive mothers screened with nasopharyngeal swabs at 24 hours of life, repeated serially up to 96 hours of life.[55] The aforementioned study by Knight in the UK reported that of a total of 265 neonates screened for the virus, approximately 5% (12/265) were positive, half of whom tested positive during the first 12 hours of life.[29]

Universal screening for COVID-19 in neonates born to asymptomatic mothers has shown unexpected results: of 418 newborns screened, 9 (2.2%) were positive for SARS-CoV-2 in the first 12 hours of life; 3 (0.7%) of whom tested positive within the first 3 hours after birth. Eight of nine mothers had negative RT-PCR tests. The only one RT-PCR positive newborn whose mother was COVID-19–positive in this case series is shown in Table 2.[48]

Table 3 summarizes results of systematic reviews focusing on congenital and intrapartum SARS-CoV-2 infections in newborns.[56–68] In the review published by Gajbhiye,[61] the frequency of neonates born to COVID-19–positive mothers testing positive for SARS-CoV-2 via either RT-PCR or antibody tests was 7.6% (24/313); while Lopes-Sousa found a lower prevalence, with 1.8% (9/493).[64] A secondary analysis undertaken by Gajbhiye[61] that only took into account neonates diagnosed within the first 48 hours

**Table 2: Neonates of COVID-19–positive mothers who tested positive for SARS-CoV-2 in the first 48 hours of life, for whom timing of infection can be determined**

Reference	Vivanti [31]	Marzollo & Facchetti [32,33]	Kulkarni [34]	Buonsenso [35]	Zamaniyan [36]	Kirstman [37]	Patanè [38]	Patanè [38]	Sisman [9]
Country	France	Italy	India	Italy	Iran	Canada	Italy	Italy	USA
Study type	RC	RC/OD	RC	SC	RC	RC	SC	SC	RC
Evidence Quality	Good	Good/Good	Good	Fair	Good	Good	Good	Good	Good
Mothers (No.)	1	1	1	1	1	1	1*	2*	1
Maternal symptoms	S-M	S-M	S-M	S-M	S-SC	S-M	S-M	S-M	S-M
GA (weeks)	35	38	38	35	32	35	37	35	34
Birth type	C	V	V	C	C	C	V	C	V
RT-PCR, NP/OT	(+)	(+)	(-)‡	(+)	(+)	(+)	(+)	(+)	(+)
RT-PCR, vaginal secretions	(+)	No	NS	NS	(-)	(+)	NS	NS	NS
RT-PCR, breast milk	NP	NS	NS	(+)	NS	(+)	NS	NS	No
Newborn (No.)	1	1	1	1	1	1	1*	2*	1
Apgar 1/5/10 min	4/2/7	9/10	6/9	8/9	8/9	9/9	9/10	9/10	7/9
Neonate symptoms	S	S	S	A	S	S	A	A	S
RT-PCR , cord/cord blood	(+)	NS	(+)	(+)	(-)	No	NP	NP	No
RT-PCR, NP/OT	(+)	doubtful at birth, later (+)	(+)	(-)	(-) at birth, later (+)	(+)	(+)	(-) at birth, later (+)	(+)
Birth-1 <sup>st</sup> sample (+) (h)	1	36	At birth	At birth	24	At birth	At birth	7 d	24
RT-PCR, rectal/stool	(+)	(+)	NS	NS	NS	(+)	NS	NS	NS
RT-PCR over time (hours or days)	Blood and BAL <6 h (+). NP & rectal (+) 3 d. CSF(-) 3 d	Tracheal aspiration (+) 72 h, NP (+) 17d & rectal (+) 19 d	NP (+) 5 and 10 d	NP (-) 1 and 5 d	2 NP (+) at 1 week	NP (+) 48 h and 7 d; Plasma and stool (+) 4 d	NP (+) 24 h and 7d	NS	NP (+) 48 h and 14 d
RT-PCR, AF	(+)	No	NS	NS	(+)	NS	NS	NS	No
RT-PCR, placenta/membranes	(+)	No	(+)	(+)	No	(+) (Surface of the maternal and fetal side, parenchyma and chorion)	(+)	(+)	NS
Evidence of SARS-CoV-2 in placenta (specific technique)	(+) (EM, IS SARS-CoV-2 N-protein)	(+) (EM, IS, SARS-CoV-2 N & S-proteins, ISH)	NS	NS	NS	Inconclusive findings (EM)	(+) (EM, ISH)	(+) (EM, ISH)	(+) (EM, IS SARS-CoV-2 N-proteins)
SARS-CoV-2 IgG/IgM at birth	NS	No	NS	NS	NS	NS	No	No	NS
Classification	Confirmed congenital	Confirmed congenital	Confirmed congenital	Confirmed congenital	Probable congenital	Probable congenital	Probable congenital	Probable congenital	Probable congenital

CR: case report CS: case series DO: descriptive/observational S-SC: symptoms-severe or critical S-M: symptoms-mild S-NS: symptoms- severity not specified GA: gestational age PT: preterm FT: full-term C: cesarean V: vaginal (+): positive (-): negative NS: not specified RT-PCR: real-time polymerase chain reaction S: symptomatic A: asymptomatic NP: nasopharyngeal OP: oropharyngeal Secr ET: endotracheal secretion IgG: immunoglobulin G IgM: immunoglobulin M NA: not apply IP: intrapartum PP: postpartum BAL: bronchoalveolar lavage CSF: cerebrospinal fluid ABA: bronchoalveolar aspirate RT-ddPCR: reverse transcription droplet digital polymerase chain reaction EM: electron microscopy ISH: in-situ hybridization IS: immunostaining IgG: immunoglobulin G IgM: immunoglobulin M \*Different mothers or newborns reported from a same study \*\*Number of mothers or newborns ‡serological studies positive for SARS-CoV-2

found a frequency of 8.0%, which constitutes an estimate of the frequency of infections acquired either congenitally or intrapartum.

A systematic review by Dhir[66] also using criteria developed by Shah[4] includes 58 newborns diagnosed positive for COVID-19 by RT-PCR, regardless of whether or not the mother was positive. Frequency of infections acquired congenitally, intrapartum or postpartum was 6.9% (4/58), 0.0% (0/58) and 70.7% (41/58), respectively. In 22.4% (13/58) of newborns, the timing of infection could not be determined.

Another systematic review examing all newborns confirmed positive for SARS-CoV-2 by RT-PCR, which did consider

either maternal COVID-19 status or the child’s age at diagnosis, found 112 neonates whose infection timing was known, 29.5% (36/122) corresponding to congenital or intrapartum infections, and the remainder to infections acquired postpartum. Of these 36 infants, in 30.6% (11/36) the timing of infections (congenital or intrapartum) was classified as confirmed. In 25/36 (69.4%) the timing of infections was classified as probable or possible. In addition to the 112 infants assessed in this analysis, the review included another 54 infants for whom it was not possible to specify the timing of infection due to insufficient data in the original articles.[67] Authors of this systematic review used the classification scheme developed by Shah.[4]

(Continuation of Table 2)

Reference	Carosso [39]	Dong [40]	Zeng H [41]	Zeng H [41]	Gao [42]	Hinojosa-Velasco [45]	Martínez-Pérez [46]	Schwartz [47]	Schwartz [47]	McDevitt [48]
Country	Italy	China	China	China	China	Mexico	Spain	Iran	Iran	USA
Study type	CR	CR	CS	CS	CR	CR	CS	CS	CS	DO
Evidence quality	Fair	Fair	Fair	Fair	Good	Good	Poor	Poor	Poor	Fair
Mothers (No.)	1	1	1*	2*	1	1	3**	1*	2*	1
Maternal symptoms	S-M	S-SC	S-NS	S-NS	S-NS	S-SC	A/S-M	S-SC	S-NS	A
GA (weeks)	37	34	ND	NS	38	38	PT 2, GA NS 1	34	34	42
Birth type	V	C	C	C	C	C	V 2, C 1	C	C	C
RT-PCR, NP/OP	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
RT-PCR, vaginal secretions	(-)	(-)	NS	NS	NS	NS	NS	NS	NS	NS
RT-PCR, breast milk	(-)	(-)	NS	NS	NS	(+)	NS	NS	NS	NS
Newborn (No.)	1	1	1	2	1	1	3†	1	2	1
Apgar 1/5/10 min	9/10	9/10	8-9/9-10	8-9/9-10	8/9	8/9	5 min >5 in 2 and <5 in 1	4/5	9/10	NS
Neonatal symptoms	1	1	1*	2*	1	1	3**	1*	2*	1
RT-PCR, cord/cord blood	(-)	NS	(-)	(-)	(-)	No	NS	NS	NS	NS
RT-PCR, NP/OP	(+)	(-)	(-)	(-)	(-)	(+)	(+)	(+)	(+)	(+)
Birth-1 <sup>st</sup> sample (+) (h)	At birth	NA	NA	NA	NA	At birth	At birth	2	1	9
RT-PCR, rectal/stool	NS	NS	NS	NS	(-)	(+)	NS	NS	NS	NS
RT-PR over time (hours or days)	NP (-) 37 h	5 tests (-) from 2 h to 15 d	NS	NS	NP and rectal (-) 7 d. RT-ddPCR (+) 7 d	Stool (+) 4 d, NP y stool (-) 13 d	NP (-) 2 d	NS	NS	No
RT-PCR, AF	No	NS	NS	NS	(-)	NS	NS	NS	NS	NS
RT-PCR, placenta/membranes	(-)	NS	NS	NS	(-)	No	NS	NS	NS	NS
Evidence of SARS-CoV-2 in placenta (specific technique)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SARS-CoV-2 IgG/IgM at birth	(+/-)	+/+	+/+	+/+	+/+	NS	NS	NS	NS	NS
Classification	Possible intrapartum	Possible congenital	Possible congenital	Possible congenital	Possible congenital	Probable intrapartum	Possible intrapartum	Possible intrapartum	Possible intrapartum	Possible intrapartum

CR: case report CS: case series DO: descriptive/observational S-SC: symptoms-severe or critical S-M: symptoms-mild S-NS: symptoms- severity not specified GA: gestational age PT: preterm FT: full-term C: cesarean V: vaginal (+): positive (-): negative NS: not specified RT-PCR: real-time polymerase chain reaction S: symptomatic A: asymptomatic NP: nasopharyngeal OP: oropharyngeal Sec ET: endotracheal secretion IgG: immunoglobulin G IgM: immunoglobulin M NA: not apply IP: intrapartum PP: postpartum BAL: bronchoalveolar lavage CSF: cerebrospinal fluid ABA: bronchoalveolar aspirate RT-ddPCR: reverse transcription droplet digital polymerase chain reaction EM: electron microscopy ISH: in-situ hybridization IS: immunostaining IgG: immunoglobulin G IgM: immunoglobulin M \*Different mothers or newborns reported from a same study \*\*Number of mothers or newborns †serological studies positive for SARS-CoV-2

An article currently in publication summarizes the largest number of COVID-19–positive mothers and their newborns (1787 mother–child pairs). Only 2.7% (49/1787) of newborns tested positive.[68] However, diagnostic criteria are not specified. This percentage is similar to that found by Lopes-Sousa,[64] at 1.8% (9/493) and its authors confirm that this percentage is similar to the frequency of newborns (2/71) affected in the three previous coronavirus epidemics (SARS-1, MERS, HKCoV/SARS), in which the only two neonates reported were diagnosed during the HKCoV/SARS epidemic. Both reviews [64,68] assume these to be cases of vertical transmission.

A meta-analysis by Kotlyar[7] includes newborns with diagnoses of COVID-19 in the first 48 hours after birth born to women diagnosed with COVID-19 in their third trimester of pregnancy. The authors found that frequency of vertical infection varies according to diagnostic method: nasopharyngeal (3.2%, 27/936),

placental (7.7%, 2/26), serological (3.7%, 3/82) or umbilical cord blood samples (2.9%, 1/34).

In our review, we identified 53 reports of COVID-19 cases diagnosed in the first 48 hours of life. The rates of infections acquired either congenitally or intrapartum were 24.5% (13/53) and 15.1% (8/53), respectively, in addition to 15.1% (8/53) whose infection timing was classified as postpartum. The timing of infection could not be determined in 45.3% (24/53) This was due to the decision by the authors to classify all cases via strict adherence to the classification criteria established for this study, with the aim of gaining precision in classifying cases, especially those acquired either in-utero or during birth (Figure 2).

Epidemiological analyses have confirmed the possibility of intrauterine or intrapartum SARS-CoV-2 transmission, but the frequency of presentation is low. Even in COVID-19–positive

(Continuation of Table 2)

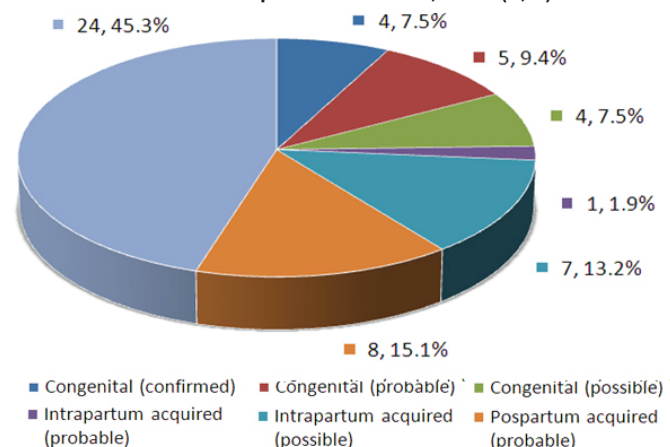
Reference	Zeng L [49]	Zeng L [49]	Zeng L [49]	Bordbar [50]	Lorenz [51]	Sinelli [52]	Pierce-Williams [53]	Gregorio-Hernández [54]
Country	China	China	China	Iran	Germany	Italy	USA	Spain
Study type	DO	DO	DO	CR	CR	CR	DO	CS
Evidence quality	Fair	Fair	Fair	Good	Good	Good	Fair	Good
Mothers (No.)	1*	2*	3*	1	1	1	1	1
Maternal symptoms	S-M	A	A	A	S-L	A	S-SC	S-M
GA (weeks)	40	40	31	NS	40	FT	NS	38
Birth type	C	C	C	C	V	V	NS	V
RT-PCR, NP/OP	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
RT-PCR, vaginal secretions	NS	NS	NS	NS	NS	NS	NS	NS
RT-PCR, breast milk	NS	NS	NS	NS	NS	NS	NS	NS
Newborn (No.)	1*	2*	3*	1	1	1	1	1
Apgar 1/5/10 min	NS	NS	3/4/5	8/9	9/9	9/10	NS	NS
Neonatal symptoms	S	S	S	S	S	S	A	S
RT-PCR, cord/cord blood	NS	NS	NS	No	NS	NS	NS	No
RT-PCR, NP/OP	(+)	(+)	(+)	(+)	(+)	(+)	(-) 24 h, after (+)	ABA (+)
Birth-1 <sup>st</sup> sample (+) (h)	48	48	48	48	±48	48–72	48	≥48
RT-PCR, rectal/stool	(+)	(+)	(+)	NS	(+)	NS	NS	NS
RT-PR over time (hours or days)	NP (+) 4 d and (-) 6 d	NP (+) 4 d and (-) 6 d	NP (+) 4 d and (-) 7 d	NP (-) >4 d	NP and rectal (+) 14 d	NP (+) 15 and 21 d	NS	NS (-) 8 d
RT-PCR, AF	NS	NS	NS	NS	NS	NS	NS	NS
RT-PCR, placenta/membranes	NS	NS	NS	NS	NS	NS	NS	NS
Evidence of SARS-CoV-2 in placenta (specific technique)	NS	NS	NS	NS	NS	NS	NS	NS
SARS-CoV-2 IgG/IgM at birth	NS	NS	NS	NS	NS	NS	NS	NS
Classification	Probable postpartum	Probable postpartum	Probable postpartum	Probable postpartum	Probable postpartum	Probable postpartum	Probable postpartum	Probable postpartum

CR: case report CS: case series DO: descriptive/observational S-SC: symptoms-severe or critical S-M: symptoms-mild S-NS: symptoms- severity not specified GA: gestational age PT: preterm FT: full-term C: cesarean V: vaginal (+): positive (-): negative NS: not specified RT-PCR: real-time polymerase chain reaction S: symptomatic A: asymptomatic NP: nasopharyngeal OP: oropharyngeal Sec ET: endotracheal secretion IgG: immunoglobulin G IgM: immunoglobulin M NA: not apply IP: intrapartum PP: postpartum BAL: bronchoalveolar lavage CSF: cerebrospinal fluid ABA: bronchoalveolar aspirate RT-ddPCR: reverse transcription droplet digital polymerase chain reaction EM: electron microscopy ISH: in-situ hybridization IS: immunostaining IgG: immunoglobulin G IgM: immunoglobulin M \*Different mothers or newborns reported from a same study \*\*Number of mothers or newborns ‡serological studies positive for SARS-CoV-2

cases identified during the first 48 hours of life, incidence of vertical transmission represents less than half of all cases, although it should be noted that this figure could be biased as it was not possible to determine the timing of infection in almost half of all cases.

**Possible mechanisms driving SARS-CoV-2 vertical transmission** The mechanisms by which SARS-CoV-2 can cause

**Figure 2: Distribution according to timing of infection. SARS-CoV-2-positive neonates diagnosed during the first 48 hours of life born to COVID-19-positive mothers, N=53 (n,%)**



congenital or intrapartum infections are still unknown. In congenital SARS-CoV-2, there are currently four proposed pathways of infection: 1) direct infection of the syncytiotrophoblast and introduction through the syncytial layers via certain receptors, specifically angiotensin-converting enzyme 2 (ACE2) and Fc receptors; 2) exposure to extravillous trophoblasts or other placental cells through maternal circulation; 3) viral passage through cells in the placenta; and 4) ascending infection through the maternal vaginal tract and cervix. In intrapartum infections, one of the main mechanisms of transmission appears to be through maternal vaginal secretions.[69,70] Aspiration of amniotic fluid or maternal blood at birth has also been considered. [8,14]

Epidemiological studies have not demonstrated increased risk of miscarriage for COVID-19-positive women.[29] Placental changes consisting of defects in the proliferation and formation of chorionic villi, typical of early stages of pregnancy, occur in a similar proportion to the rate of SARS-CoV-2 infections in the first trimester of pregnancy, which might suggest a correlation between these two rare phenomena. In more advanced stages of pregnancy, placental insufficiency and its direct consequence, intrauterine hypoxia, become more important from both pathophysiological and epidemiological standpoints. Research suggests that placental insufficiency and intrauterine hypoxia occur in 20% (9/45) of pregnancies involving COVID-19-positive mothers.[68]



**Table 3: Systematic reviews of SARS-CoV-2 vertical transmission in living newborns**

Author	Study period	Articles included (No.)	COVID-19–positive neonates/total No. of neonates with COVID-19–positive mothers (%)	Diagnostic criteria	Number of neonates with congenital or intrapartum infections*/ COVID-19–positive neonates (%)
Chi[56]	Dec/2019–Mar/2020	14	7/90† (8.8)‡	RT-PCR or IgM	1/7 (14)
Fornari[57]	Jan/2020–Mar/2020	9	5/70 (7.1)	RT-PCR or IgM	1/5 (20)
Durán[58]	Dec/2019–Apr/2020	20	16/NS	RT-PCR or IgM	3/16 (18)
Cabero-Pérez[59]	Dec/2019–Apr/2020	33	13/381 (3.4)	RT-PCR or IgM	3/13 (23)
Cavalcante de Melo[60]	Dec/2019–May/2020	38	16/432 (3.7)	RT-PCR or IgM	1/16 (6)
Gajbhiye[61]	Dec/2019–May/2020	50	24/313†(8)	RT-PCR or specific antibodies	21/261 (8) <48 h
Gordon[62]	Dec/2019–May/2020	8	10/NS‡	RT-PCR	0
Pettirosso[63]	Dec/2019–May/2020	61	13/717 (1.8)	RT-PCR, nasopharyngeal	2/13 (15)
Lopes-Sousa[64]	Dec/2019–May/2020		9/493 (1.8) + 3 IgG(+) and IgM(+) neonates	RT-PCR	1/9 (11)
Kotlyar[7]§	Dec/2019–May/2020	69	27/936† (3.2)	RT-PCR or IgM	9/27 (33)
Thamir Ahmed[65]	Jan/2020–Jun/2020	19	8/125 (8.1)‡	RT-PCR	2/8 (25)
Dhir[66]	Dec/2019–Jun/2020	32	39/1005† (3.9)‡ They identified 58 neonates with or without COVID-19–positive mothers	RT-PCR	4/58 (6.9)
Raschetti[67]	Dec/2019–Jul/2020	74	176/NS	RT-PCR, nasopharyngeal or IgM	Vertical infection: 36/122 (29.5) Congenital: 15/122 (12.2) Intrapartum acquired 21/122 (17.3)
AbdelMassih[68]	Nov/2019–Aug/2020	66	49/1787 (2.7)	NS	According to the authors: 19/49 (38.8) positive at <12 h; 7/49 (14.3) positive between 12–24 h. Total <24 h 26/49 (53)

\*According to modified criteria by Shah et al.[4] †Number of newborns tested ‡Patients who recur in different studies were excluded §Includes only COVID-19–positive neonates diagnosed at ≤48 h after birth || Includes meta-analysis of vertical transmission NS: not specified IgG: immunoglobulin G IgM: immunoglobulin M

Placental studies of women diagnosed with COVID-19 in their third trimester have shown signs of poor maternal and fetal vascular perfusion in fetuses and newborns negative for SARS-CoV-2.[69] Studies of COVID-19–positive neonates have shown chronic intervillitis with macrophage infiltrates at the placental level.[38] This was also the case in the placenta of a dead fetus, also COVID-19–positive.[71] Evidence of placental SARS-CoV-2 by in situ hybridization, immunostaining or visualization of viral particles by transmission electron microscopy in newborns whose nucleic acid tests were negative suggests that even in cases where SARS-CoV-2 is present in the placenta, the risk of vertical transmission is limited.[70,72]

The placenta constitutes an immunological barrier guarding against vertical transmission of pathogens, which could minimize colonization of the syncytiotrophoblast and subsequent transmission of SARS-CoV-2 to the fetus. An important immunomodulatory factor is the maternal–fetal interface, which is composed in turn of the decidua derived from the mother and the placenta derived from the fetus.[73]

ACE2 expression is extensive in the female genital tract and in the fetoplacental unit. ACE2 expression varies during the stages of pregnancy; via RNA sequencing of individual cells, some authors have found that it tends to increase as gestation progresses,[74] while others report ACE2 messenger RNA expression is higher in placental cells during the early phases of pregnancy.[75]

Analysis of transcriptomes in placental cells has shown low co-expression levels of ACE2 receptors and transmembrane-serine protease 2 (TMPRSS2), suggesting that the virus may use other pathways to enter placental cells, which could differ from the pathways currently being suggested.[76]

Facchetti[33] analyzed expression of SARS-CoV-2 spike proteins (S) in 101 placentas using immunohistochemical techniques. Of the 101 placentas, 15 belonged to mothers who tested positive for COVID-19. Of all the placentas studied, only one—belonging to a newborn with pneumonia who had previously been described as positive for SARS-CoV-2—showed high expression of viral S and nucleocapsid (NC) proteins in the syncytiotrophoblast.[32] SARS-CoV-2 RNA was detected in syncytiotrophoblast and intervillous inflammatory cells by in situ hybridization, and particles morphologically consistent with the novel coronavirus were visualized by electron microscopy in the cytoplasm of syncytiotrophoblast cells, the endothelium of fetal capillaries, fibroblasts and mononuclear cells. High expression of S and NC viral proteins were found in areas of dense inflammation, with a predominance of monocytes and macrophages, as well as in maternal and fetal villous cells. These findings suggest that infections can spread via circulating viruses present in infected fetal mononuclear cells, after recruitment of maternal inflammatory cells, without resulting in villitis. The fact that this was found in only 1 of the 101 placentas examined in the study also supports the notion that vertical transmission of SARS-CoV-2 via the transplacental route is a rare event.

The rarity of this phenomenon has also been suggested by results of other research. Hecht studied 19 placentas from mothers with COVID-19 and detected presence of SARS-CoV-2 by in situ hybridization in only 2.[13] Examinations using immunohistochemical techniques demonstrated ACE2 expression differs from that of TMPRSS2 in placentas of women who contracted COVID-19 during pregnancy. ACE2 was localized in the syncytiotrophoblast, away from maternal blood sources and mainly in the stroma. TMPRSS2 was present only and sparsely in the villous endothelium and rarely in the syncytiotrophoblast. Taglauer[77] visualized the location and relative abundance of the SARS-CoV-2 spike glycoprotein and the colocalization of the ACE2 and TMPRSS2 proteins using comparative immunofluorescence in placental samples from 15 pregnant women with COVID-19, 5 of whom showed evidence of vertical transmission. In cases with and without evidence of vertical transmission, there was evidence of the presence of the SARS-CoV-2 spike glycoprotein in the villous compartment of placental tissues and predominance of ACE2 protein expression over TMPRSS2 protein expression. Both ACE2 and spike glycoproteins were consistently expressed in the outer layer of the syncytiotrophoblast of placental villi, in juxtaposition with placental regions associated with maternal blood flow.

The fact that viremia has been found in only 1% of COVID-19 patients[78] also supports the proposition that vertical transmission of SARS-CoV-2 via the transplacental route is a rare event.

The impact of disease severity in the mother on the likelihood of congenital infection is still under discussion. It has been suggested that congenital infection could be more frequent in cases of women with severe or critical infections,[24] and less frequent after a short-term exposure to the virus in the early stages of fetal development. Speculative explanations have been proposed based on viral incubation periods and the limitations of diagnostic tests.[14] However, a recent study reports presence of SARS-CoV-2 in chorionic villi endothelial cells and, to a lesser extent, in trophoblasts, in COVID-19–positive pregnant women with mild manifestations of the disease.[79] Maternal comorbidities such as preeclampsia, diabetes mellitus and other diseases that can influence expression of ACE2 receptors, as well as certain HLA haplotypes and polymorphisms of immunoregulatory genes, should be taken into account.[70]

In our review, in eight of nine confirmed or probable cases of congenital infection, maternal disease was mild, which seems to suggest that congenital infection can occur regardless of the severity of maternal presentation; or perhaps might even be more common in children born to mothers with mild symptoms. A retrospective cohort study from a US hospital shows that severe or critical infection in the mother was not associated with vertical transmission of COVID-19.[80]

Transmission of protective antibodies from mother to fetus through the placenta could provide a tentative explanation for the lower proportion of congenital infections in newborns of mothers with severe or critical illness presentations found in this review; however there is no certainty regarding the role of antibodies transferred from the mother. Although some of these antibodies can neutralize viral particles, others facilitate their capture by cells with a high presence of Fc receptors, such as endothelial and syncytiotrophoblast cells, which would favor transplacental viral transmission.[70] Asymptomatic neonates or neonates presenting with mild symptoms born to women with COVID-19 confirmed either via nucleic acid

tests or serology have presented with elevated levels of anti-SARS-CoV-2–specific IgG but negative RT-PCR tests.[81]

## PERSPECTIVES

More studies are required on intrauterine and intrapartum SARS-CoV-2 transmission, and larger datasets are required before we can estimate the incidence of this phenomenon or perform causality analyses. Some registries have been working in this direction and various initiatives have emerged to catalogue vertical transmission.[2,29,82]


Current mathematical modeling suggests that combining drug-based therapies with vaccines could optimize treatment of diseases capable of both vertical and horizontal transmission.[83]

Although it is premature to propose drugs to prevent maternal-fetal transmission of SARS-CoV-2 and its effects on pregnancy, drugs that can influence levels of gene expression or enzymatic activity of ACE2 could be potential candidates. However, a better understanding is still needed of the ACE2-receptor contribution to facilitating viral entry into placental cells.[76,84] Passive immunization could be another option, due to its potential for minimizing effects of maternal viral infection in gestational products and in the fetal systemic inflammatory response.[85]

An ideal proposal would involve active immunization of pregnant women, but historically, pregnant and lactating women have not been included in such studies for safety reasons. It is possible that effective vaccination of the general population will prevent SARS-CoV-2 infection in pregnant women through herd immunity. New proposals have been forwarded allowing for the use of vaccines in pregnant women during epidemics of emerging diseases, including WHO support for recommendations in 2019 by the Working Group on Research Ethics in Pregnancy, Epidemics and New Technologies.[86,87] Nevertheless, before considering vaccination of pregnant women, the short- and long-term effects of COVID-19 on pregnancy, as well as on fetuses and newborns, should be investigated, as sufficient information is lacking. Related elements for further research are the type of vaccine to be used (platform, adjuvants, immunogenicity, toxicological analysis, etc.) and the likelihood of vaccine acceptance in this population group.

The main limitation of this review is the high level of uncertainty that persists regarding the timing of infection, which could not be determined in all cases. The strengths of the review lie in the novelty of the case-by-case analysis, the use of a new classification system, the decision to include only newborns of COVID-19–positive mothers who tested positive for the virus in the first 48 hours after birth or near this time limit, and the extensive review of articles published in both Spanish and English.

## CONCLUSIONS

Congenital and intrapartum SARS-CoV-2 infection in the fetus/newborn is possible, but rare. In the published literature, among newborns of COVID-19–positive mothers who tested positive in the first 48 hours of life, congenital and intrapartum infections account for just over a third of all infections. We recommend undertaking international collaborative studies at the population level using standardized instruments to determine the frequency of vertical transmission of SARS-CoV-2. 

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