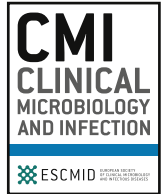




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Research note

Congenital infection of SARS-CoV-2 in live-born neonates: a population-based descriptive study

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ABSTRACT

Objective: To evaluate the evidence of mother-to-child transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: This is a descriptive, multicentre, observational study in nine tertiary care hospitals throughout Spain. The study population was women with coronavirus disease 2019 during pregnancy. Mother-to-child transmission was defined as positive real-time RT-PCR of SARS-CoV-2 in amniotic fluid, cord blood, placenta or neonatal nasopharyngeal swabs taken immediately after birth.

Results: We included 43 women with singleton pregnancies and one with a twin pregnancy, as a result we obtained 45 samples of placenta, amniotic fluid and umbilical cord blood. The median gestational age at diagnosis was 34.7 weeks (range 14–41.3 weeks). The median interval between positive RT-PCR and delivery was 21.5 days (range 0–141 days). Fourteen women (31.8%, 95% CI 18.6%–47.6%) were positive at the time of delivery. There was one singleton pregnancy with SARS-CoV-2 RT-PCR positive in the placenta, amniotic fluid and umbilical cord blood (2.2%, 95% CI 0.1%–11.8%). Nasopharyngeal aspiration was performed on 38 neonates at birth, all of which were negative (0%, 95% CI 0%–9.3%). In 11 neonates the nasopharyngeal aspiration was repeated at 24–48 hours, and one returned positive (9.1%, 95% CI 0.2%–41.3%).

Conclusions: The presence of SARS-CoV-2 in placenta, amniotic fluid and cord blood shows that mother-to-child transmission is possible but uncommon. **Itziar Garcia-Ruiz, Clin Microbiol Infect 2021;27:1521.e1–1521.e5**

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Introduction

Physiological changes in pregnancy increase the susceptibility to infections and their severity. Moreover, maternal infections may have consequences for the offspring, as obstetric complications or congenital infections.

Clinical presentation of coronavirus disease 2019 (COVID-19) in pregnancy is similar to the general population [1], but with a significantly higher risk of Intensive Care Unit admission and invasive ventilation than in non-pregnant adults [2,3].

The likelihood of mother-to-child transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still unknown. Several studies have suggested this possibility [4–6], but most of them did not have enough evidence to demonstrate both maternal and fetal or neonatal infection.

The aim of this study was to evaluate the possibility of mother-to-child transmission of SARS-CoV-2 in a cohort of pregnant women with COVID-19.

Materials and methods

Approval for the study was obtained from the Vall d'Hebron University Hospital Ethics Committee (PR(AMI)181/2020) on 27 March 2020, and subsequently validated in the other hospitals. Informed consent was obtained from pregnant women for the collection of data and biological samples from the mother and newborn.

Study population

This sub-study of the Gesta-Covid Collaborative Group (see Supplementary material, [Appendix S1](#)) included only pregnant women with COVID-19 infection for whom amniotic fluid, umbilical cord blood and placenta samples were collected at birth. Exclusion criteria were age under 18 years, difficulty understanding informed consent and refusal to participate.

A COVID-19 confirmed case was defined as laboratory confirmation of real-time RT-PCR for SARS-CoV-2 assay of the nasal and pharyngeal swab. In probable cases (negative RT-PCR), if the symptoms had started in the last 7 days then the RT-PCR was repeated after 24 hours, otherwise a serology test was performed.

Study outcomes

The primary outcome was evidence of mother-to-child transmission, defined as positive RT-PCR of SARS-CoV-2 in amniotic fluid, cord blood, placenta or neonatal nasopharyngeal swabs taken immediately after birth [7].

Clinical data

Medical and obstetric history, exposure history and COVID-19 symptoms in the previous 14 days, physical examination, and laboratory and radiological findings were collected. COVID-19 severity was classified into three groups: mild (not requiring hospital admission), severe (pneumonia) and critical (Intensive Care Unit admission).

Data on pregnancy, gestational age at delivery, mode of delivery, indication for cesarean delivery, maternal complications and neonatal outcomes were also recorded.

Newborns were examined by a paediatrician specialized in congenital infections.

Microbiological samples collection

Nasal and pharyngeal swabs were taken from the mothers on a weekly basis until negativity.

All non-respiratory samples were collected at the time of delivery with strict aseptic techniques to avoid contamination by maternal blood or by respiratory droplets from the mother or birth attendants. The procedure is described in detail in the Supplementary material ([Appendix S2](#)).

Table 1
Baseline demographic and clinical characteristics

Maternal age (years), median (range)	33.5 (18–46)
Body mass index (kg/m ²), median (range)	26.6 (16.7–47.0)
Ethnic group, <i>n</i> (%)	
Caucasian	29 (65.9%)
Latin American	12 (27.3%)
Asian	2 (4.5%)
Black-African	1 (2.3%)
Type of pregnancy, <i>n</i> (%)	
Single	43 (97.7%)
Dichorionic diamniotic twins	1 (2.3%)
Cigarette smoker, <i>n</i> (%)	1 (2.3%)
Medical condition, <i>n</i> (%)	8 (18.2%)
Autoimmune disease	4
Asthma	1
Diabetes	1
Thrombophilia	1
Acquired heart disease	1
Clinical presentation, <i>n</i> (%)	
Mild disease	29 (65.9%)
Pneumonia	12 (27.3%)
Severe pneumonia – ICU admission	3 (6.8%)
Diagnosis, <i>n</i> (%)	
RT-PCR	33 (75%)
Serology	11 (25%)
Gestational age at diagnosis (weeks), median (range)	34.7 (14–41.3)
Interval RT-PCR diagnosis and delivery (days), median (range)	21.5 (0–141)
RT-PCR positive at delivery, <i>n</i> (%)	14 (31.8%)

Abbreviations: ICU, intensive care unit.

Results

Forty-four pregnancies with samples of placenta, amniotic fluid and umbilical cord blood collected were included in the study. There was one monochorionic twin pregnancy, in which the samples were taken from both fetuses. As a result, we obtained 45 samples. Table 1 depicts baseline demographic and clinical characteristics of the studied population and Table 2 shows pregnancy outcome.

The median gestational age at COVID-19 diagnosis was 34.7 weeks (range 14–41.3 weeks). The median interval between positive RT-PCR and delivery was 21.5 days (range 0–141 days). Fourteen women (31.8%, 95% CI 18.6%–47.6%) were still positive at the time of delivery.

Table 2

Pregnancy outcome

Gestational age at birth (weeks), median (range)	39 (28.4–41.4)
Labour onset, n (%)	
Spontaneous	16 (36.4%)
Elective	28 (63.6%)
For COVID-19	2 ^a
Other indication	26
Preterm birth <37 weeks, n (%)	2 (4.5%)
For COVID-19	2 ^a
Other	0
Mode of delivery, n (%)	
Vaginal delivery	29 (65.9%)
Caesarean section	15 (34.1%)
Pregnancy outcome, n (%)	
Live births	44 ^b
Stillbirth	1 ^c
Birthweight (g), median (range)	3440 (1000–4425)

^a Two cases of preterm birth at 28 weeks and 3 days, and 36 weeks and 5 days, respectively, due to COVID-19 infection. In both cases, a caesarean section was performed because of the worsening maternal condition.

^b One was a twin pregnancy.

^c The stillbirth occurred in an asymptomatic woman who tested positive for COVID-19 at 20 weeks. The fetus was diagnosed with macrocephaly, intracranial cyst and polyhydramnios at 30 weeks, and resulted in a stillbirth at 34 weeks. The genetic study did not show any abnormal finding, and the post-mortem examination showed central nervous system anomalies (ventriculomegaly, subependymal cysts).

One singleton pregnancy was SARS-CoV-2 RT-PCR-positive in the placenta, amniotic fluid and umbilical cord blood (2.2%, 95% CI 0.1%–11.8%) Fig. 1

Nasopharyngeal aspiration was performed on 38 neonates at birth, all of which were negative (0%, 95% CI 0%–9.3%). In 11 neonates the nasopharyngeal aspiration was repeated at 24–48 hours, and one was positive (9.1%, 95% CI 0.2%–41.3%).

Discussion

Of the 45 neonates analysed, one was SARS-CoV-2 RT-PCR-positive in the placenta, amniotic fluid and umbilical cord blood, but negative in nasopharyngeal aspirate.

To accept the possibility of mother-to-child transmission of SARS-CoV-2, there are two requirements: a confident diagnostic test to confirm maternal and fetal or neonatal infection and an adequate exclusion of contamination of the samples. In our case, both conditions were met. The mother had COVID-19 confirmed by RT-PCR with clinical symptoms at delivery, and neonatal infection was proven by the detection of SARS-CoV-2 in placenta, amniotic fluid and umbilical cord blood. Strict aseptic measures were taken to collect the samples. Contamination of the placenta can be excluded by the cytoplasmic positivity of trophoblastic cells observed with antibody against SARS-CoV-2 Figs. 2 and 3. Amniotic fluid and cord blood samples are not easily susceptible to contamination by vaginal fluid or by respiratory droplets from the mother or attendants if strict sterile collection measures are taken. Moreover, the possibility of contamination of both, taken at different times, is extremely unlikely.

Several studies reported SARS-CoV-2 RT-PCR-positive results in neonatal samples within the first hours after birth [4–6], but they did not report placenta, amniotic fluid or umbilical cord blood positive samples. The link between mother and neonate infections is during labour or postnatal, but there is no evidence of longer exposition for the fetus during pregnancy. Only six studies [8–13] and ours support the possibility of intrauterine exposure and transmission to the child.

According to Shah et al. [14] classification system, only the studies by Vivanti et al. [12], Fenizia et al. [13] and us are confirmed cases of congenital infection in a live-born neonate. Other studies [4–6,8–11] may only consider possible or even unlikely congenital

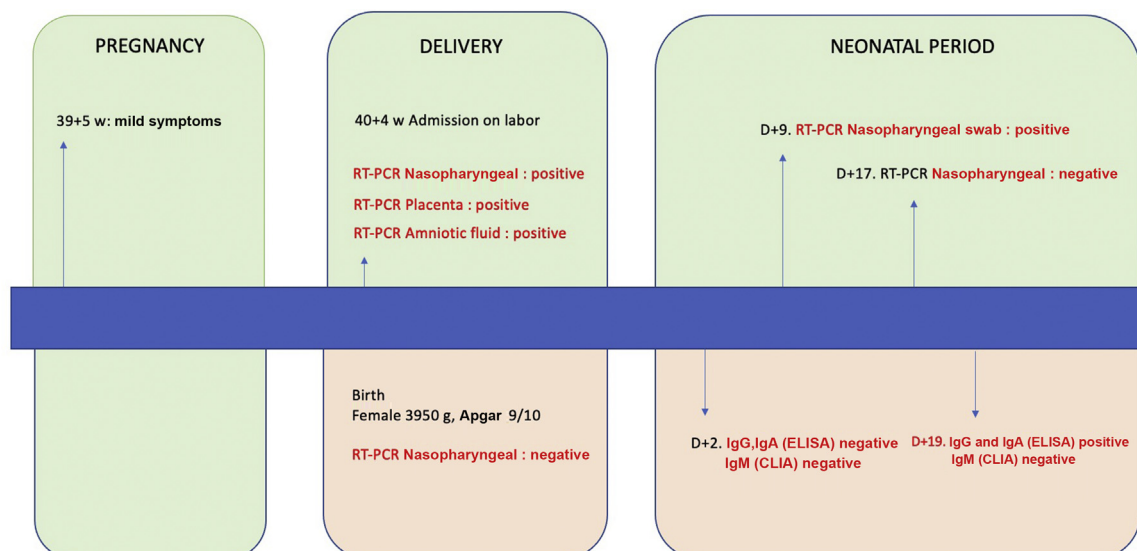


Fig. 1. Summary of the case.

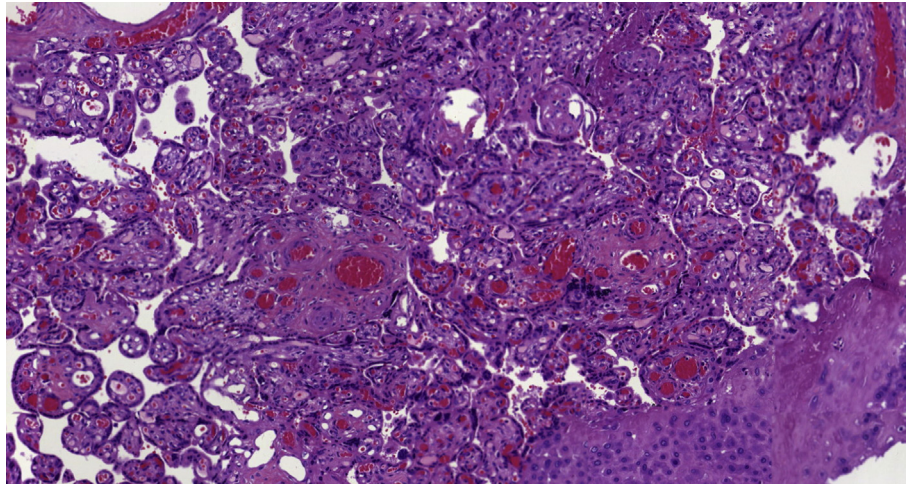


Fig. 2. Detection of SARS-CoV-2 by immunohistochemistry.

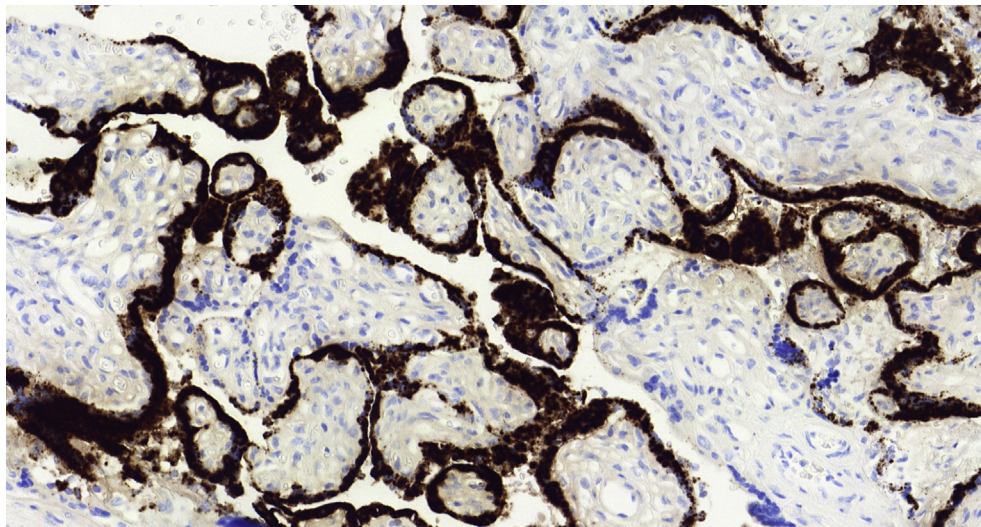


Fig. 3. Detection of SARS-CoV-2 by in situ hybridisation.

infection because there are not enough specimens from the mother or the newborn and contamination during labour or caesarean cannot be ruled out.

Our newborn nasopharyngeal RT-PCR was negative. In Vivanti et al., neonatal respiratory sample was obtained from non-bronchoscopic bronchoalveolar lavage before extubation, which is more sensitive. Testing RT-PCR in other tissues may improve the detection of the virus in neonates [15].

Neonatal antibodies were negative at birth and became positive 49 days later. It could be the response of the newborn's immune system to SARS-CoV-2 infection. However, maternal origin postnatally or cross-reactivity with non-specific antibodies can never be excluded entirely.

The sample size is small. As a result of the epidemiological time when the patients were recruited, personal protective equipment was lacking, and ethical approval was substantially delayed, making sample collection challenging. Besides, in some cases, amniocentesis was not possible because of premature rupture of membranes.

The findings of this study support the possibility of mother-to-child transmission, even it seems to be rare. A larger cohort would be necessary to accurately evaluate the rate of congenital transmission and assess the newborn's potential consequences.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Contribution to authorship

This study was conceived by IG, ES, NM and AS, who contributed to the design of the study. Collection and analysis of the data was performed by IG, BS, IF, LR, DS, MF, FC, NF, NM and AS. Analysis of

the samples was performed by ES, AA, JE and AN. Drafting the article was performed by IG, ES, NM, EC, NF and AS. All authors, IG, ES, BS, IF, LR, DS, AA, JE, MF, FC, AN, NF, NM, EC, AS and Gestacovid Collaborative Group, reviewed and agreed to the final version of the manuscript.

Details of ethics approval

This study was approved by the Vall d'Hebron University Hospital Ethics Committee (PR(AMI)181/2020) on 27 March 2020.

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Appendix

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.06.016>.

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