Maternal, Perinatal and Neonatal Outcomes With COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns During Their First Month of Life

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Background: Our aim was to describe the clinical features of mothers with coronavirus disease 2019 (COVID-19) infection during gestation or delivery, and the potential vertical transmission. We also wish to evaluate the possible horizontal transmission after hospital discharge, by means of a follow-up of all the newborns included at 1 month of age.

Methods: This multicenter descriptive study involved 16 Spanish hospitals. We reviewed the medical records of 242 pregnant women diagnosed with COVID-19 from March 13 to May 31, 2020, when they were in their third trimester of pregnancy. They and their 248 newborn infants were monitored until the infant was 1 month old.

Results: Caesarean sections (C-sections) were performed on 63 (26%) women. The initial clinical symptoms were coughing (33%) and fever (29.7%). Mothers hospitalized due to COVID-19 pathology had a higher risk of ending their pregnancy via C-section (P = 0.027). Newborns whose mothers had been admitted due to their COVID-19 infection had a higher risk of premature delivery (P = 0.006). We admitted 115 (46.3%) newborn infants to the neonatal unit, of those, 87 (75.6%) were only admitted due to organizational circumstances. No infants died and no vertical or horizontal transmission was detected. Regarding type of feeding, 41.7% of the newborns received exclusive breast-feeding at discharge and 40.4% at 1 month.

Conclusions: We did not detect COVID-19 transmission during delivery or throughout the first month of life in the newborns included in our study. Exclusive breast-feeding rates at discharge and at 1 month of age were lower than expected.

Key Words: COVID19, newborn, SARS coronavirus 2, breast-feeding, cesarean delivery

Since the beginning of the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS coronavirus 2) declared March 11, 2020, by the World Health Organization (WHO),¹ million have been infected worldwide, and hundreds of thousands have died. The infection caused by this virus appears to have a milder impact on children;² and more so in neonates, in whom, to date, vertical transmission has not been proven.¹⁶ Sporadic severe cases have been reported in this group of neonatal patients.¹⁶

Currently, there is insufficient evidence regarding a possible SARS coronavirus 2 transmission via breastmilk.¹⁵ The WHO, United Nations International Children’s Emergency Fund, and the Centers for Disease Control and Prevention continue to recommend breast-feeding in this scenario, applying basic hygienic measures.¹⁰⁻¹²

Protocols regarding how to best manage both mother and newborn have evolved day by day as the pandemic progressed and our knowledge on the matter improved. At first, recommendations included no skin to skin contact after birth and immediate newborn and mother separation.¹³,¹⁴ With passing weeks, however, these recommendations were modified to accepting skin to skin contact and permitting mother and newborn cohabitation as long as basic hygiene measures were followed,¹⁵ although this tendency has not been the same throughout different countries.¹⁶

The aim of this study was to describe the clinical features of mothers who had coronavirus disease 2019 (COVID-19) infection during gestation or delivery, and the potential vertical transmission to the newborn in this scenario. We also wish to evaluate the possible horizontal transmission after hospital discharge, by means of a follow-up of all the newborns included at 1 month of age.

MATERIALS AND METHODS

Study and Patients’ Design

We designed a multicenter, descriptive study among 16 Spanish University hospitals who were members of the newly formed Neo-COVID-19 Research Group which was established to study the impact that COVID-19 could have on newborn infants in Spain.

The study has two parts: first, we reviewed the medical records of both infected mothers and their newborns, and second, we did a follow-up of all the included newborns, at 1 month of age.

We reviewed the medical records of 242 pregnant women diagnosed with COVID-19 from March 13 to May 31, 2020, when they were in the third trimester of pregnancy. They and their newborn infants were monitored throughout their hospital stay and until the infants were 1 month of age. The inclusion criteria were: newborn of mother with COVID-19 infection confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests or serologic test and acceptance of informed consent. Women who, despite having compatible symptoms,
did not have a positive RT-PCR or serologic test results were excluded from the study.

A positive diagnosis was established according to official indications as issued by the Spanish Government. SARS coronavirus 2 RT-PCR were obtained using nasopharyngeal and/or oropharyngeal swab samples from the mothers and newborn infants. Serologic testing in pregnant women was done with enzyme-linked immunosorbent assay.

This study was reviewed and approved by the Medical Ethics Committee of Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain (approval number CP 01.20), and by the ethics committees of all other participating hospitals. Eligible mothers were informed about the study and gave informed consent. All aspects of this study were performed in accordance with the ethical standards of the Declaration of Helsinki.

Data Collection
The clinical information obtained from the mothers included: demographic data, disease history during the perinatal period, the number of days from the first COVID-19 symptoms to delivery, maternal treatment during gestation, and specific aspects about delivery.

The information collected on the newborn infants included: demographic information, Apgar test, type of resuscitation required, and any respiratory assistance needed. We also reviewed the length of hospital stay, the age when viral tests were obtained, and their results, their diagnosis at discharge, and whether they received breastmilk, donor milk, or formula throughout the different moments of follow-up (first feed, at discharge and at 1 month of age).

Newborns were considered small for their gestational age when their weight was equal or less than 10th percentile, according to PediTools electronic growth chart calculator. All newborns were discharged to their parents, who were informed of the Spanish Neonatology Society standards for avoiding transmission.

The follow-up was performed when the baby was 1 month of age. We phoned to the parents to determine whether they had required visiting the emergency ward or their primary care pediatrician, or if the baby had been hospitalized since discharge and for what reason.

Statistical Analysis
Numerical variables were expressed as means and standard deviations or medians and interquartile ranges, according to their distribution. Qualitative variables were expressed as absolute frequencies and percentages. We estimated 95% confidence intervals and assessed normal distribution by using Kolmogorov’s test. Statistical analyses were performed using Stata v.15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS
Clinical Features of the Mothers With COVID-19
A total of 242 women were included with confirmed COVID-19 infection in our study. Two hundred twenty (92.1%) had positive RT-PCR during delivery or at some point during their third trimester of pregnancy. The remaining 19 (7.8%) had negative RT-PCR tests during gestation or delivery but had compatible serologic results during labor: 6 (2.4%) had positive IgM and IgG, and 13 (5.3%) had negative IgM and positive IgG. They were diagnosed at a mean gestational age of 37.3 $\pm$ 3.1 weeks of gestation.

The most frequently presented symptoms during gestation or labor were coughing (33%) and fever (29.7%). Odynophagia (2.4%) and chest pain (1.6%) were uncommon (Table 1). Only seven patients required intensive care (2.9%), including one mother who died due to a massive thromboembolic event. In most cases, treatment received during pregnancy included hydroxychloroquine (16.1%). Darunavir (1.6%) or cobicistat (0.8%) were used only in exceptional cases. No side effects from these medications were observed in the newborn infants.

Caesarean sections (C-sections) were performed on 63 women (26%) and the mothers’ clinical deterioration due to COVID-19 was the indication in six patients (9.5%), who represented 2.4% of all the pregnancies. Failure to progress (25.3%) was the most common indication for a C-section, followed by abnormal presentation (23.8%), repeated C-sections (12.6%), and presumed fetal compromise (12.6%).

Mothers hospitalized due to COVID-19 pathology, had a higher risk of ending their pregnancy via C-section, OR 2.15 (CI 95%, 1.09-4.25, P = 0.027). Companions were allowed during labor in 39.2% of the cases.

Clinical Features of Neonates Born to COVID-19 Mothers
Most of the 248 neonates were term infants. Thirty-six were preterm (14.5%) and 21 of those were late preterm babies (58.3%). Only four (1.6%) were born with less than 32 weeks gestation. Newborns whose mothers had been admitted strictly due to their COVID-19 infection had a higher risk of premature delivery, OR 2.95 (95% CI, 1.37-6.41, P = 0.006).

We admitted 115 newborn infants (46.3%) to the neonatal unit and their median stay was 3 (interquartile range [IQR] 2–10) days. Of those 115 admissions, 87 (75.6%) were only admitted for intermediate care due to organizational circumstances, namely...
because the mother had been admitted to a dedicated COVID-19 area rather than the maternity ward. At the time this article was written, two of these patients were still in the neonatal intensive care unit due to their prematurity and their clinical features are shown in Table 2.

We carried out RT-PCR tests on nasopharyngeal and/or oropharyngeal swab samples in 230 cases (92.7%). It was not done in 18 newborns (7.2%) because their mothers’ had negative RT-PCR at labor. Re-tests were carried out on 87 of the 248 infants (35%) at a median age of 48 hours (IQR 38–48). A third test was only obtained in six cases at a median age of 53 hours (IQR 35–72).

The results were positive in the first sample for 11 newborn infants (4.4%); two were born by C-section and nine had vaginal deliveries. One of these patients was a 33-week preterm infant, while the rest (90.9%) were born at term. In six of these (54.5%), skin to skin contact had been allowed and babies remained with their mothers. The newborn infants’ mothers had been admitted based on the COVID-19 criteria in four cases, but with only mild to moderate symptoms, and they had all tested RT-PCR positive during delivery. The median age at which the first PCR was obtained in this group of patients was 18 hours (range 2–24). Clinical outcome was good in all cases: none presented with pneumonia or any other clinical feature compatible with SARS-CoV-2 infection. A second PCR was obtained in this group at a median age of 47.5 hours (24–72 h), all of which resulted negative.

Results were positive in the second sample in two newborn infants (0.8%), one of which had been immediately separated from his mother after birth. Both had negative first samples and had remained asymptomatic thereafter. All other tests in the infants came back negative.

The vast majority, 222/248 (89.5%) did not need any respiratory support and surfactant therapy was only used in three infants (1.2%) due to their prematurity. Twenty-six patients (10.5%) were diagnosed with transient tachypnea and 17 of these were preterm infants (65.3%). There was one case of hypoxic-ischemic encephalopathy. There were no cases of pneumonia and pneumothorax.

There were four other diagnoses not related to COVID-19: one case of polymalformation syndrome with esophagus and duodenal atresia, one case of pulmonary malformation that presented with shock, one case of necrotizing enterocolitis in a 33-week preterm baby, and one case of hemolytic disease of the newborn. There were no deaths.

In 136 cases, (54.8%) the newborn infants received their own mother’s milk at birth.

**Follow-up of Neonates Born to COVID-19 Mothers**

Of the 248 infants recruited, 235 (94.7%) completed the follow-up when the infant was 1 month of age. During this period, 23 patients (9.7%) visited the emergency ward (two of them on two occasions) at a median age of 14 days (4–30). They were diagnosed with: baby colic (n = 4), jaundice (n = 3), fever (n = 2), common cold (n = 2), convulsions (n = 1), suspected choking (n = 1), and rhinitis (n = 1). In 10 cases (43.4%), they did not have any recognizable pathologic feature. RT-PCR was performed in five babies, due to compatible clinical manifestations (two with fever, two with common cold symptoms, and one with rhinitis) with negative results in all cases.

Three patients required admission to hospital during their first month of age (1.2%); one due to urinary tract infection and two presenting with fever without a source with negative blood cultures, neither of whom required respiratory or vasoactive support. There were no deaths reported during our follow-up.

Regarding type of feeding, 40.4% of the newborns who completed the 1-month follow-up were receiving exclusive breast-milk (Table 2).

**DISCUSSION**

This study describes the clinical features of 242 pregnant women infected with COVID-19 and their 248 infant newborns, at birth and during their first month of life. The clinical presentation in pregnant women in our study was similar to what other groups have recently published.4,19 Requiring intensive care during pregnancy is infrequent, although it has been described in literature as an exceptional event.19,20 Similarly, death due to COVID-19 in pregnant women is very rare, and only a few sporadic cases have been published.21,22 More than half of the women in our study were completely asymptomatic before delivery, which is a higher rate than the 32.6% that Smith et al23 describe in their systematic review or what Zaigham et al20 published in their review.

Most women did not require pharmacologic treatment for their COVID-19 infection during pregnancy. When deemed necessary, the preferred options, as officially recommended,24,25 were hydroxychloroquine, azithromycin, and antiretroviral treatment.

During the first stages of the pandemic in China, C-section was the most common mode of delivery with a rate of almost 90%.26,27,28 With time, C-section indications in COVID-19 infected mothers have been gradually reduced to scenarios with maternal or

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**Table 2. Clinical Features of the 248 Neonates Born to Mother With COVID-19**

<table>
<thead>
<tr>
<th>Clinical features of neonates</th>
<th>Gestational age in weeks, median (IQR)</th>
<th>Weight in grams, mean and SD</th>
<th>Weight percentile &lt;40th, n (%)</th>
<th>Head circumference (cm), mean and SD</th>
<th>Male n (%)</th>
<th>Twins n (%)</th>
<th>Delivery room</th>
<th>Age at first virus test in hours, median (IQR)</th>
<th>Need for respiratory support, n (%)</th>
<th>Nasal continuous positive airway pressure, number (%)</th>
<th>High-flow nasal cannula, number (%)</th>
<th>Mechanical ventilation, n (%)</th>
<th>Neonatal symptoms</th>
<th>Initial type of feeding</th>
<th>Type of feeding at discharge (n = 247)</th>
<th>Type of feeding at 1 month (n = 235)</th>
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<td>39 (38–40)</td>
<td>3084 ± 605</td>
<td>29 (11.6%)</td>
<td>33.9 ± 2</td>
<td>129 (52%)</td>
<td>13 (5.2%)</td>
<td>Appgar score at one minute, median (IQR)</td>
<td>28 (10.4%)</td>
<td>21 (8.4%)</td>
<td>9 (3.6%)</td>
<td>3 (1.2%)</td>
<td>Respiratory distress, n (%)</td>
<td>Own mother’s milk, n (%)</td>
<td>Exclusive breast-feeding, n (%)</td>
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<td>Appgar score at five minutes, median (IQR)</td>
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<td>Jaundice, n (%)</td>
<td>Formula, n (%)</td>
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<td>Advanced resuscitation*</td>
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<td>Digestive intolerance, n (%)</td>
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<td>Subsequently admitted to neonatal ward, n (%)</td>
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<td>Subsequently admitted to intermediate care, n (%)</td>
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<td>Own mother’s milk, n (%)</td>
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<td>Subsequently admitted to intensive care unit, n (%)</td>
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<td>Donated breastmilk, n (%)</td>
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**COVID-19 indicates coronavirus disease 2019; IQR, interquartile range; SD, standard deviation. Advanced resuscitation was defined as needing positive pressure ventilation or nasal continuous positive airway pressure at birth, intubation, or vasoactive drug administration.”**
fetal compromise, following current obstetric guidelines. In our study, we detected a higher risk of having a C-section in those mothers who had required hospitalization due to COVID-19 complications. It is unclear whether maternal deterioration in relation to the infection is the cause for C-sections and accounts for the poor outcomes, or if this mode of delivery in itself worsens outcomes in infected mothers.

Evidence regarding a possible vertical transmission is, to date, limited. We detected 11 positive RT-PCR results in the first samples that were negative in the following samples. We also found two positive results in the second sample tests: both neonates had previous negative results, and neither had any symptoms. We, therefore, considered them to be false positives.

Prematurity rate was higher in our study than expected in standard conditions, more so in mothers who required admission due to the COVID-19 infection. Other scientific publications have detected a higher rate of prematurity in pregnant women with COVID-19 infection. However, prematurity could derive from needing to end the gestation due to maternal COVID-19-related complications, and not specifically due to direct intrauterine infection.

Neonates born from COVID-19 infected mothers mostly present with uncomplicated symptomatology: respiratory distress, fever, and coughing, although sporadic sepsis-like cases have been described. Clinical outcome is generally good in all cases, and hypoxic-ischemic encephalopathy (HIE) is exceptional. In our study, we describe only one newborn with HIE, with a negative RT-PCR, whose mother was asymptomatic and diagnosed with COVID-19 during labor. We do not consider this ischemic event to be a consequence of COVID-19 infection. Most patients in our study were asymptomatic or had only mild symptoms, mainly due to their underlying diseases. There were no deaths during the immediate neonatal period.

There is insufficient evidence regarding the possible transmission of SARS coronavirus 2 via maternal breastmilk. although sporadic sepsis-like cases have been described. Clinical outcome is generally good in all cases, and hypoxic-ischemic encephalopathy (HIE) is exceptional. In our study, we describe only one newborn with HIE, with a negative RT-PCR, whose mother was asymptomatic and diagnosed with COVID-19 during labor. We do not consider this ischemic event to be a consequence of COVID-19 infection. Most patients in our study were asymptomatic or had only mild symptoms, mainly due to their underlying diseases. There were no deaths during the immediate neonatal period.

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There has been controversy in this regard, however, various organizations related to the newborn’s health have maintained their recommendations to promote breast-feeding in COVID-19 infected mothers, as long as hygiene and protection measures can be ensured to prevent possible horizontal transmission in the postnatal period. In our study, less than half of the newborns were receiving exclusive breast-feeding at discharge, as was the case at 1 month of age. Initial measures that were applied throughout the pandemic such as not allowing skin to skin contact after birth, or mother-newborn separation, together with other factors such as work overload, maternal anxiety, and fear of infecting their babies could have seriously influenced this outcome. The impact of maternal-newborn separation on breast-feeding and the newborn’s health has been clearly documented: early separation limits total duration of breast-feeding interferes with mother and newborn bonding increases the risk of maternal stress during hospitalization and doubles the necessary hospital resources.

We detected a slightly higher rate of visits to the emergency ward compared with other published data for this group of age, although these were related to common causes for consultation in neonates, and we did not observe significant illness in any case. Those who required admission to hospital did so for common causes in this group of age, and none had COVID-19 infection. There were no deaths in our study during our follow-up. Based on this, we believe that correct implementation and follow-up of hygiene recommendations given at discharge can be effective in preventing horizontal transmission in this group of patients.

The limitations of our study are the following: during the first week of the study, the data were obtained retrospectively, although the proportion of these cases (3.6% of the total sample) we believe does not interfere with the global results. Another limitation is that criteria for studying mothers with RT-PCR varied throughout the study period, so we cannot rule out the possibility that asymptomatic infected mothers were not detected in the first weeks. Also, the sensitivity of the diagnostic test has proven to be limited. The virus has not been tested in the placenta, amniotic fluid, or umbilical cord blood, so we cannot completely rule out the possibility of vertical transmission. Finally, RT-PCR was not repeated throughout the first month of life in all the studied newborns. This implies we cannot confirm the complete absence of infection in all the babies.

**CONCLUSIONS**

We did not detect COVID-19 transmission during delivery or throughout the first month of life in the newborns included in our study. Exclusive breast-feeding rates at discharge and at 1 month of age were lower than expected. Considering the proven benefits of breast-feeding on both the mothers’ and newborns’ health, we believe it is crucial to find new strategies to improve the proportion of these newborns that receive breastmilk in their first days of life and onwards.

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