Clinicolaboratory Profile of and Outcomes in Neonates Born to COVID-19–Positive Mothers

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Abstract

**Background and Aims:** The novel coronavirus (COVID-19) infection and its mode of transmission, clinical manifestations, treatment, and outcomes are not studied much in newborns. Hence, the aim of this study was to find out the proportion of COVID-19–positive neonates born to COVID-19–positive mothers and to assess clinicolaboratory profile of and outcomes in neonates born to COVID-19–positive mothers.

**Materials and Methods:** This was a hospital-based retrospective observational study conducted from April 13, 2020, to July 31, 2020, at the NICU of a tertiary care hospital. A total of 120 neonates born to COVID-19–positive mothers were enrolled in this study. These neonates were monitored for COVID-19 symptoms, investigated (using throat swab reverse transcriptase polymerase chain reaction [RT-PCR] test), and treated, if required. \( \chi^2 \) test was used for statistical analysis.

**Results:** The male-to-female ratio was 3:2 in the study population. Of the 120 neonates, 15% were preterms, 25% were of low birth weight, and 55.8% were delivered through vaginal deliveries. Only 5 (4.2%) of the 120 neonates tested positive for COVID-19. The COVID-19–positive neonates remained asymptomatic and were discharged after 2 consecutive negative RT-PCR reports. The first RT-PCR sample was sent at NICU admission, and the second RT-PCR sample was sent at 72 hours after the first positive report. In case of a nonconclusive
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Current Topic

The entire world is fighting against the novel coronavirus (COVID-19) pandemic currently. COVID-19 is caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2, which was first noticed in China in December 2019 and started spreading rapidly worldwide. On January 30, 2020, the WHO declared this virus outbreak a public health emergency. According to the WHO situation report, as on January 5, 2021, in India, there have been 10,356,844 confirmed positive cases of COVID-19 with 149,850 deaths.¹ There was an assumption in the initial days of the outbreak that children are not at a high risk of COVID-19 infection. However, lately there were incidents of COVID-19 infection in children, but of a mild course.² Similarly, little is known about COVID-19 infection in pregnant women and fetuses.³ Not much information is available regarding outcomes and management of the mothers and neonates affected by COVID-19.³,⁴ Neonates may be infected either through transplacental transmission during the intrauterine period or during the postnatal period (from mother, caregiver, and/or during hospitalization). There is not much established evidence regarding vertical transmission. However, a neonatal infection due to postnatal transmission is described.⁷ Availability of literature on clinical manifestations associated with COVID-19, epidemiology, and outcomes in neonates is limited.

Aims

The primary aim of this clinical study was to find out the proportion of COVID-19–positive neonates born to COVID-19–positive mothers. The secondary objectives were to study the clinicolaboratory profile and outcomes in neonates born to COVID-19–positive mothers. Leukopenia, lymphopenia, and raised levels of C-reactive protein (CRP), fibrin degradation products (FDPs), and D-dimer were the main laboratory findings in COVID-19–positive neonates. All the COVID-19–positive neonates remained asymptomatic during the study. Vaginal delivery did not increase the risk of COVID-19 infection. The mean duration of COVID-19 positivity, hospital stay, and viral clearance was 5.4, 10, and 5.6 days, respectively, in our study.

Key Words: COVID-19, novel coronavirus, newborns, pregnancy, vaginal delivery, fibrin degradation products, D-dimer
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Laboratory parameters of and outcomes in neonates born to COVID-19–positive mothers.

Materials and Methods

Study design

This was a hospital-based retrospective observational study conducted from April 13, 2020, to July 31, 2020, in the NICU of Mahila Chikitsalaya (Sanganeri Gate; Department of Pediatrics, Sawai Man Singh [SMS] Medical College, Jaipur, Rajasthan, India).

Inclusion criteria

All neonates delivered by COVID-19–positive pregnant women and admitted at the NICU of our institution were included in the study.

Exclusion criteria

Neonates delivered by COVID-19–negative mothers and whose parents refused to give informed written consent were excluded from the study. In addition, intrauterine deaths and stillbirths were also excluded.

Study procedure

Deliveries of COVID-19–positive pregnant women were attended by pediatricians involved in the study with all safety measures in labor rooms of Mahila Chikitsalaya that was dedicated to treat COVID-19–positive patients. After resuscitation, all neonates were admitted to the NICU of the same institution. The neonates were monitored for vital parameters including oxygen saturation. Throat swab samples were collected at two time points (ie, the first sample within 24 h and the second at 72 h of postnatal age) and sent for reverse transcriptase polymerase chain reaction (RT-PCR) test to check whether the neonates were positive for COVID-19. Other investigations including complete blood count (CBC), C-reactive protein (CRP), liver function tests, renal function tests, blood glucose, serum calcium, X-ray of the chest, serum ferritin, procalcitonin, D-dimer, fibrin degradation products (FDPs), and prothrombin time were also done. The neonates were assessed for fever, rhinorrhea, irritability, rash, diarrhea, and feed intolerance during their hospital stay. Treatment for all medical illnesses was given as per the institutional protocol. All the neonates were followed up at least once until their discharge (on day 14). Maternal information such as demographics, household contacts, and clinical presentation was noted from hospital bedside tickets. The mothers were also assessed for symptoms such as fever, cough, shortness of breath, sore throat, myalgia, vomiting, diarrhea, anosmia, and ageusia.

Feeding policy

In the study plan, there was no guideline on direct breastfeeding and skin-to-skin contact of neonates with their COVID-19–positive mothers. The mothers and their newborns were kept separately. The neonates were given expressed breast milk (EBM) and formula feed in case of nonavailability of EBM. After both the mother and her neonate tested negative for COVID-19, breastfeeding was allowed and they were kept together. Thereafter, breastfeeding was encouraged and reinforced at discharge and at follow-up.

Infection control measures

Infection control measures were followed during data collection, while carrying the neonates away from the mother, and while feeding neonates with EBM or formula to prevent its spread. All medical personnel maintained hand hygiene and used personal protective equipment during the study.

The following case definitions were used in the study:

(A) A suspected COVID-19–positive pregnant woman

1. A pregnant woman with respiratory symptoms with a history of international travel in the last 14 days
2. A pregnant woman in contact with COVID-19 patients
3. A pregnant woman working as a health care professional caring for COVID-19 patients
4. A symptomatic or asymptomatic pregnant woman coming from cluster zone/hot spot

(B) A COVID-19–positive pregnant woman
1. A pregnant woman with nasopharyngeal swab testing positive for COVID-19 in RT-PCR test before delivery
2. A pregnant woman’s nasopharyngeal swab suspected positive for COVID-19 in RT-PCR test after delivery

(C) A COVID-19–negative neonate: A neonate delivered by a COVID-19–positive pregnant woman who tested negative for COVID-19 twice in RT-PCR test

(D) A COVID-19–positive neonate: A neonate whose throat swab tested positive once for COVID-19 in RT-PCR test

(E) Discharge criteria: As per our institutional protocols and NNF Kerala guidelines

The neonates were enrolled for the study after obtaining informed written consent from their parents. The study was approved by the institutional ethics committee.

Statistical analyses

Data were analyzed by using descriptive statistics as well as inferential statistics. Appropriate tests such as frequencies, percentage, mean, and $\chi^2$ tests were used. Results were computed using SPSS 22.0 (trial version, IBM SPSS Trials, Jaipur, Rajasthan, India) and Microsoft Excel 2010.

Results

During the study period, 120 COVID-19–positive pregnant women delivered at our hospital. All neonates of these mothers were admitted to the NICU and screened for COVID-19. Their oropharyngeal swabs were analyzed using RT-PCR test. Five neonates tested positive for COVID-19, and 115 neonates tested negative for COVID-19. The maternal demographics and contact with symptomatic COVID-19–positive patients are shown in Table 1. Demographics, clinical characteristics, and outcomes of the neonates are given in Table 2. Blood investigation reports of COVID-19–positive neonates are shown in Table 3. Postnatal age at the time of RT-PCR test results of COVID-19–positive neonates is shown in the Figure.
Table 3. Blood Investigations of the COVID-19–Positive Neonates

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Newborn 1</th>
<th>Newborn 2</th>
<th>Newborn 3</th>
<th>Newborn 4</th>
<th>Newborn 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Leukocyte Count (10^9/L)</td>
<td>3.4</td>
<td>3.6</td>
<td>15.6</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Total Platelet Count (10^11/L)</td>
<td>3.86</td>
<td>4.93</td>
<td>4.67</td>
<td>2.22</td>
<td>2.82</td>
</tr>
<tr>
<td>SGOT, U/L</td>
<td>64</td>
<td>73.4</td>
<td>112</td>
<td>129</td>
<td>46</td>
</tr>
<tr>
<td>SGPT, U/L</td>
<td>32</td>
<td>41.9</td>
<td>81</td>
<td>87</td>
<td>51</td>
</tr>
<tr>
<td>C-Reactive Protein, mg/dL</td>
<td>15</td>
<td>21</td>
<td>13</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Prothrombin Time, s</td>
<td>14.8</td>
<td>16.1</td>
<td>15.4</td>
<td>14.2</td>
<td>14.8</td>
</tr>
<tr>
<td>D-dimer, ng/mL</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum LDH, U/L</td>
<td>186</td>
<td>180</td>
<td>184</td>
<td>162</td>
<td>174</td>
</tr>
<tr>
<td>Serum Ferritin, ng/mL</td>
<td>302</td>
<td>384</td>
<td>296</td>
<td>475.9</td>
<td>287</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>0.18</td>
<td>0.14</td>
<td>0.26</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>FDPs, mg/mL</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>PT/INR</td>
<td>1.3</td>
<td>1.4</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

FDP, fibrin degradation product; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Outcomes

All the COVID-19–positive neonates (n = 5) remained asymptomatic, and all were discharged after two consecutive negative RT-PCR tests. The average duration of hospital stay in our study was 10 days. Apart from COVID-19 symptoms, of the 115 COVID-19–negative neonates, 5 neonates (4.4%) had transient tachypnea of the newborn (TTNB), 2 (1.7%) had septicemia, 1 (0.9%) had birth asphyxia, and 107 (93.0%) were healthy. Of the 115 neonates, 8 (7.0%) required oxygen, 112 (97.4%) were discharged, and 3 (2.6%) died during the study.

Discussion

To our knowledge, this is the largest Indian study on neonates born to pregnant women who were COVID-19 positive at the time of delivery. These neonates were subsequently treated and followed up till 14 days after discharge.

In our study, 70% of the pregnant women had a history of contact with symptomatic COVID-19–positive patients, while in Salvatore et al’s study, only 60% of the patients had household contacts. Household contact included husband (50%) and other family members (20%) in our study (Table 1). None of the enrolled pregnant women had a history of international travel within the last 14 days before hospitalization. Majority of the COVID-19–positive pregnant women (75%) were asymptomatic in our study and were found to be positive for COVID-19 on contact tracing. Only one-fourth of the pregnant women were symptomatic showing symptoms such as cough, cold, fever, myalgia, nausea, malaise, anosmia, and ageusia. The duration of the symptoms was less than a week in most of the pregnant women at the time of hospitalization. Whereas in Salvatore et al’s study, 38% of pregnant women showed symptoms for < 7 days and rest of them had symptoms for > 7 days. In our study, similar to Salvatore et al’s
study, use of masks and any degree of hand hygiene maintenance were noted in all the pregnant women.

All the neonates born to COVID-19–positive pregnant women were admitted to the NICU and tested for COVID-19 as soon as possible (ie, within 24 h of delivery or within 24 h of the mother testing positive for COVID-19, whichever was earlier). Of the 120 neonates, 115 (95.8%) tested negative and 5 (4.2%) tested positive for COVID-19. Similarly, a recent study found 3 of the 45 neonates positive for COVID-19 in their study. In contrast to our study, in Salvatore et al’s study, all the 120 newborns (100%) were negative for COVID-19.

Risk factors such as advanced age, diabetes, hypertension, chronic medical illnesses, asthma, and use of steroids were noted in COVID-19–positive pregnant women. Symptoms and severity of COVID-19 in all these women were noted. We looked for any risk factors or higher severity in the mothers of the COVID-19–positive neonates (n = 5), but we did not find any, although we did not test the viral load of COVID-19 in these mothers. The mothers of 3 (60%) of the 5 COVID-19–positive neonates had contact with more than one family member who was positive for COVID-19. Similar to our study, De Bernardo et al observed that 20% of neonates in their study had both mothers and fathers and, in other cases, grandparents also being positive for COVID-19. The possibility of third parties infecting neonates cannot be excluded.

In our study, the mean duration of postnatal first-time COVID-19 positivity was 5.4 days with a range of 3 to 9 days, which is similar to a recent systematic review. But De Bernardo et al observed a relatively higher disease onset duration, that is, 8.2 ± 8.5 days (range: 1–25 d). None of the neonates turned COVID-19 positive in the initial 48 hours of birth in our study, as in Salvatore et al’s study. In contrast to our study, case reports by Zamaniyan et al and Zeng et al reported neonates testing positive for COVID-19 within 48 hours of birth.

All the COVID-19–positive neonates were observed for symptoms during their hospital stay, and all remained asymptomatic. In contrast to our study, De Bernardo et al observed fever (28%), vomiting (16%), cough or shortness of breath (12%), diarrhea, lethargy or respiratory difficulty (8%) or cyanosis, and other symptoms such as feed intolerance, intercostal retractions, mottling, and sneezing in COVID-19–positive neonates. A recent meta-analysis revealed that COVID-19–positive neonates were symptomatic and required intensive care unlike children aged 1 to 19 years.

In our study, CBC, CRP, erythrocyte sedimentation rate (ESR), serum ferritin were tested and X-ray of the chest was done in all the enrolled neonates, while D-dimer and FDP were evaluated only in COVID-19–positive neonates. In COVID-19–negative neonates (n = 115), the blood tests (CBC, CRP, ESR, and serum ferritin) and X-ray of the chest were normal. Whereas in COVID-19–positive neonates, we found leukopenia (total leukocyte count [TLC] < 4000/mm3) and lymphopenia (< 1100/mm3) in 80%, severe lymphopenia (< 5% of TLC) in 20%, and high CRP (> 6 mg/dL) in 60%. D-dimer and FDP values were also found to be high in 60% and 40% of COVID-19–positive neonates, respectively. A study showed normal or decreased leukocyte counts or decreased lymphocyte counts. However, it remained partly unexplained why the neonates remained asymptomatic despite raised levels of acute phase reactants. This may have clinical implications for better monitoring and early initiation of treatment before any clinical worsening. The average duration of hospital stay was 10 days in our study similar to a recent systematic review.

The mothers and their neonates were kept away from each other after delivery as per the recommendations formulated by the American Academy of Pediatrics, Centers for Disease Control and Prevention, and Chinese expert consensus. To decrease the risk of perinatal transmission, they advise to isolate the neonates immediately after delivery, provide formula feed or EBM, and maintain no contact, if possible. This recommendation is in contrast to the recommendation by the WHO, UK Royal College of Obstetricians and Gynaecologists, Italian Society of Neonatology, and European Neonatal and Perinatal Societies, which advocate the promotion of breastfeeding and the initial
skin-to-skin contact. Moreover, recently, Groß et al. reported detection of SARS-CoV-2 in breast milk.

As per the guidelines, in our study, the neonates were given EBM or formula feed in case of nonavailability of EBM. After both the neonate and the mother tested negative for COVID-19, direct breastfeeding was allowed, and they were kept together. Thereafter, breastfeeding was encouraged and reinforced at discharge and at follow-up after 14 days (at least once or as required based on the neonates’ condition). Breastfeeding rates were 30% and 70% at discharge and follow-up, respectively.

Majority of the neonates (95.8%) born to COVID-19–positive mothers were COVID-19 negative in our study. Although they did not have symptoms related to COVID-19, they had other illnesses, that is, 4.4% had TTNB, 0.9% had birth asphyxia, and 1.7% had septicemia; and the remaining 93.0% were healthy. Similar to our study, 92% of neonates were asymptomatic in a study conducted by Davanzo et al, and 100% were asymptomatic in Liu et al’s study. In our study, 2.6% of the COVID-19–negative neonates died due to birth asphyxia (0.9%) and septicemia (1.7%). Liu et al and Zhu et al observed mortality in 8% and 10% of the neonates, respectively. In our study, 2.6% of the COVID-19–negative neonates died due to birth asphyxia or septicemia; the remaining 95.8% were healthy. Similar to our study, 92% of neonates were asymptomatic in a study conducted by Davanzo et al, and 100% were asymptomatic in Liu et al’s study. In our study, 2.6% of the COVID-19–negative neonates died due to birth asphyxia (0.9%) and septicemia (1.7%). Liu et al and Zhu et al observed mortality in 8% and 10% of the neonates, respectively, in their studies.

The COVID-19 positivity rate was only 4.2% in neonates born to COVID-19–positive mothers, whereas it was 0% in studies conducted by Chen et al (n = 9), Li et al (n = 17), Zhu et al (n = 10), and Chen et al (n = 4). Zeng et al (n = 33) reported the COVID-19 positivity rate in neonates to be 3 (9.1%) between days 2 and 4. Wang et al’s study reports of 1 neonate who was born to a COVID-19–positive mother and tested positive at 36 hours.

In our study, the neonatal outcomes were good and hence all the COVID-19–positive neonates were discharged after two consecutive negative RT-PCR tests. In Salvatore et al’s study, 89% of the neonates were discharged at 5 to 7 days of life, and 9 remained hospitalized. Similar to our study, De Bernardo et al also observed a good prognosis, with lesser complications and no deaths, in COVID-19–positive neonates. Treatments were prevalently symptomatic or supportive. Oxygen was supplied to only 7.0% of the neonates in our study, similar to studies by Chen et al, Liu et al, and Li et al. Neonates were discharged to a healthy asymptomatic caregiver and were closely followed up for 2 weeks after discharge. The mean viral clearance duration was 5.6 days with a range of 2 to 10 days. We took viral clearance time from the first positive report to the first negative report as all neonates remained asymptomatic. The overall risk of COVID-19 infection in neonates during in utero, natal, or postnatal period is not clear. We did not do RT-PCR tests for placental tissues as in Salvatore et al’s study. As none of the neonates tested positive for COVID-19 in the initial 2 days of life, we could not make any inference regarding vertical transmission.

In our study, 55.8% of the neonates were delivered via the vaginal route similar to that in Salvatore et al’s study (56%). In contrast to our study, Chen et al, Zeng et al, Liu et al, and Li et al reported higher cesarean section deliveries—77%, 100%, 100%, and 88%, respectively. In our study, we found that vaginal delivery did not increase the risk of COVID-19 positivity. The strengths of our study include a large sample size and 100% follow-up rate till 14 days after discharge. Limitations were a relatively small period of follow-up (14 days) and not evaluating transmission of the virus through breast milk, cord blood, and placenta. So far, this has been the only Indian study conducted with a large sample size.

Conclusion

According to our study, vaginal delivery did not increase the risk of COVID-19 in neonates. The proportion of neonates born to COVID-19–positive women was very low (P = 4.2). Leukopenia, lymphopenia, and raised values of CRP, D-dimer, and FDP were the main laboratory findings in COVID-19–positive neonates. All the neonates, irrespective of their COVID-19 status, delivered by COVID-19–positive women remained asymptomatic. The mean duration of COVID-19 positivity, hospital stay, and viral clearance was 5.4, 10, and 5.6 days, respectively, in our study.
References


