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Original Article

Clinical profiles of neonates born to mothers with COVID-19

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Abstract

Background The risk of congenital infections in neonates born to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected mothers and those breastfed by infected mothers remains largely unknown.

Objective To describe the outcomes and clinical features of neonates born to mothers infected with SARS-CoV-2 during pregnancy, to follow up neonates who were positive for SARS-CoV-2 at the time of delivery for a period of 1 month, and to identify potential risk factors associated with disease transmission.

Methods This prospective observational study on neonates born to SARS-CoV-2-infected mothers between June 2020 and January 2021 was carried out after getting written informed consent in a tertiary care government hospital (Government Medical college Kannur, North Kerala, India). The clinical and demographic characteristics of infected mothers were reviewed. Neonates were tested for SARS-CoV-2 infection within 24 hours of birth, with repeat testing on day 5 for those who were negative at birth. The demographic and clinical characteristics as well as potential risk factors for disease transmission in these neonates were evaluated.

Results A total of 342 neonates (95.3%) were tested for SARS-CoV-2 infection at birth. Rooming-in and breastfeeding was practiced in 75% of at-risk neonates. Fifty neonates tested positive for SARS-CoV-2 infection at birth (14.3%); 293 neonates who tested negative at birth remained so on day 5, except one baby isolated with a caretaker who also tested positive, indicating postnatal infection. There was no statistically significant increased risk of infection in neonates born to SARS-CoV-2-positive mothers compared to those born to mothers who had already become negative at delivery. Mild symptoms were present in 8% of positive neonates. On one-month follow up, all neonates were well and gaining weight.

Conclusion Vertical transmission, in particular transplacental, may be possible in SARS-CoV-2-infected mothers. Maternal infection at the time of delivery is not a predictor for increased vertical transmission compared to mothers whose infections had resolved prior to delivery. Breastfeeding with appropriate hygiene measures is not a risk factor for horizontal transmission. **[Paediatr Indones. 2021;61:277-82 ; DOI: 10.14238/pi61.5.2021.277-82**].

Keywords: *SARS CoV-2 infection; mothers; neonate; outcome; vertical transmission; breastfeeding; horizontal transmission*

Very little is known about the effects of SARS-CoV-2 infection on fetuses and newborns.[1] Reports suggest that children have less severe clinical symptoms when infected.[2] However, infants seem to have higher severity of illness in the pediatric age group.[3] The rate of congenital infections of neonates born to SARS-CoV-2-positive mothers remains unknown. Intrauterine vertical transmission may occur transplacentally or through ingestion or aspiration of cervicovaginal secretions.[4] The neonate's risk of developing COVID-19 during the perinatal period, especially when breastfeeding is also unknown.[1]

We aimed to describe the outcomes and clinical features of neonates born to mothers infected with SARS-CoV-2 during pregnancy. We also followed up neonates who were positive for SARS-CoV-2 at the time of delivery for a period of 1 month to identify potential risk factors associated with disease transmission.

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Methods

In this prospective observational study, all neonates born to mothers with SARS-CoV-2-positive nasopharyngeal swab test during pregnancy, irrespective of gestational age, between June 2020 and January 2021 at Government Medical College Kannur, Kerala, India, were included. Maternal details were noted, such as gestational age at the time of SARS-CoV-2 diagnosis, symptoms of COVID-19 infection, SARS-CoV-2 test result status at the time of delivery, i.e., confirmed SARS-CoV-2 infection within 10 days before delivery, and if negative, the interval between delivery and the day of becoming negative. Ultrasound abnormalities, fetal distress, and mode of delivery were also recorded

Neonates were tested for SARS-CoV-2 by real-time reverse transcriptase polymerase chain reaction (RT-PCR) on a nasopharyngeal swab specimen as early as possible, within 24 hours of birth if the mother had SARS-CoV-2 infection within 14 days before delivery. Rapid antigen test was done by nasopharyngeal swab at 5 days for those negative at birth.[5] In addition, neonates' demographic and clinical characteristics were evaluated.

In the initial 1-2 months of the study, at-risk neonates were kept in a separate isolation room with a caretaker and given formula feeds until mothers were declared free of infection, as per the hospital policy. But with a surge in the number of cases and resulting lack of available rooms, all newborns, unless medically indicated, roomed in with mothers and were allowed to breastfeed after appropriate counseling on hand hygiene, breast cleansing, and use of a surgical mask.[5] The newborns with confirmed SARS-CoV-2 infection were followed up to 1 month for symptoms, immunization status, and growth assessment.

Descriptive analysis results are presented as proportions. Chi-square test was used and P values <0.05 were considered to be significant. Calculations were done using *Microsoft Excel software*. This study was approved by Institutional Ethics Committee of Government Medical College, Kannur.

Results

During the study period there were a total of 1,042 deliveries. Of 353 (10.9%) mothers positive for SARS-CoV-2 infection, 352 (99.7%) were positive in the 3rd trimester and 236 mothers (66.8%) were positive at the time of delivery, as shown in **Figure 1**. The mean gestational age was 37 weeks + 2 days, with a standard deviation of 2 weeks + 2 days. Thirty (8.5%) mothers had symptoms of SARS-CoV-2 infection. Symptoms included fever, cough, headache, myalgia, sore throat, rhinitis, breathlessness, diarrhea, and anosmia. One mother required ICU admission and ventilator support, but she succumbed to the illness.

Intrauterine growth restriction (IUGR) was detected in 1.4% mothers by antenatal ultrasound. One hundred two (28.9%) mothers delivered vaginally and 251 mothers (71.1%) underwent Caesarean section (CS). Previous CS was the most common indication of CS (29%), followed by fetal distress and non-stress test (NST) abnormalities (13.6%).

Of 359 newborns, there were 6 pairs of twins, 197 males (54.9%), 56 (15.6%) with fetal distress, as well as 44 (12.3%) preterm and 39 (10.9%) small-for-gestational age (SGA) babies. Fifteen (4.2%) babies had an abnormal APGAR score, i.e., <7 at 1 minute. Sixteen (4.5%) infants required some form of resuscitation in the form of tactile stimulation: (6 babies; 1.7%), bag and mask ventilation (8; 2.2%), and intubation and ventilation (2; 0.6%) babies.

Among the neonates, 6 (1.7%) had respiratory distress syndrome, 15 (4.2%) had transient tachypnoea of newborn, 6 (1.7%) had feed intolerance, 5 (1.4%) had early onset sepsis, 1 (0.3%) had perinatal asphyxia, 2 (0.6%) had meconium aspiration syndrome, and 16 (4.5%) babies required phototherapy for neonatal jaundice.

Of the 342 babies (95.3%) who were born to mothers infected within 14 days of delivery and tested for SARS-CoV-2 infection, 50 (14.6%) were found to be positive; 29 (59.2%) of them were born to mothers who were positive at the time of delivery. Chi-square test revealed no significant difference in the risk of infection in neonates born to mothers positive for SARS-CoV-2 infection at delivery compared to mothers who had already become negative at the time of delivery ($P=0.06$). Among the infected neonates, 20 (40.8%) were born to mothers who were negative at the time of delivery. The proportion of positive neonates born to mothers delivered within 7 days of becoming COVID-19-negative was 15 (21.4%) and that of positive neonates born within 7-14 days of becoming negative

was 5 (16.7%). The Z-test for difference between two proportions revealed no significant difference, as all of them were negative on day 10 by rapid antigen test. One baby who was negative at birth turned positive on day 5 by rapid antigen test and became negative after 10 days. The 292 babies who were negative at birth remained negative on day 5 of life.

The maternal and neonatal characteristics of positive babies are depicted in **Tables 1** and 2, respectively.

The majority of positive neonates were asymptomatic and exclusively breastfed, while 4 (8%) had mild symptoms. Mothers were called for follow up when infants were 1 month of age. However, only 2 infants visited the outpatient department for follow up, while the remainder were followed up by phone. All 50 babies were thriving well, had adequate development for age, and had received routine immunizations, though delayed in all. The child with neonatal seizures had normal MRI and EEG results and was kept under follow-up.

Discussion

To our knowledge this is the largest cohort of neonates born to SARS-CoV-2-infected mothers and studied in Kerala, India. The test positivity rate in this study was 14.6%. This rate was 6.5% in a cohort of 185 neonates tested after 72 hours6, 10.7% in a cohort of 65 neonates of which only 2 were tested within 24 hours (3.1%),[7] 3.9% in a meta-analysis of 58 neonates,[8] and 3.3% in a multicenter study from Turkey with infants tested after 48 hours.[9]

The risk of vertical transmission has been an enigma, but recently published reports suggest evidence of vertical transmission.[10] Such evidence would include testing of placental tissue, amniotic fluid before membrane rupture, umbilical cord blood, neonatal blood in the first 12 h, and neonatal throat/nasopharyngeal swab for RT-PCR in the immediate postpartum period.[11] The SARS-CoV-2 positivity within 24 hours of life indicates a high probability of congenital infection. However, infection in mothers at the time of delivery as well as delivery within 7 days of becoming negative was not associated with infection

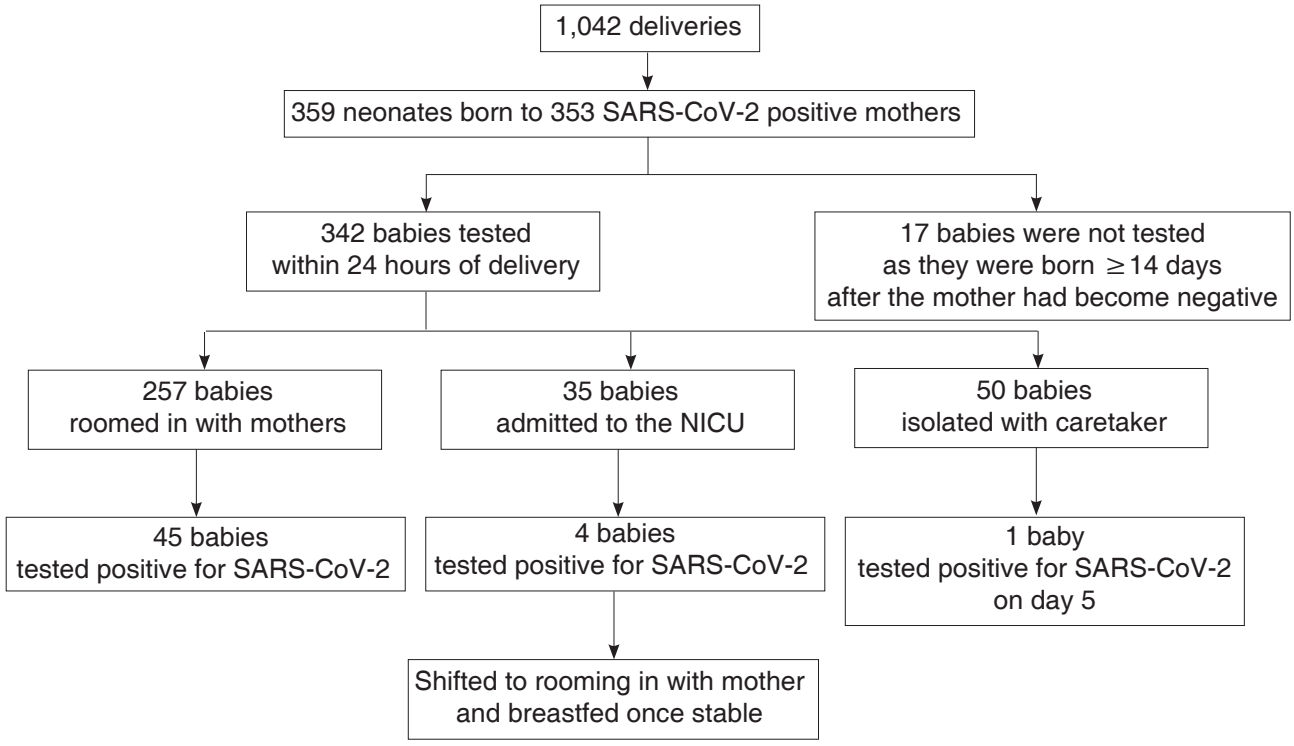

Figure 1. Study flow chart of maternal and infant SARS-CoV-2 testing

Table 1. Comparison of characteristics of mothers with SARS-CoV-2-infected neonates and without SARS-CoV-2-infected neonates

Maternal characteristics	Non-infected neonates (n=303)	Infected neonates (n=50)
Mean gestational age at the time of testing positive (SD), weeks+days	37+2 (2+3)	37+6 (1+2)
Maternal symptoms present, n (%)		
Yes	27 (8.9)	3 (6)
No	276 (91.1)	47 (94)
Maternal symptoms, n (%)		
Fever	14(4.6)	2(4)
Sore throat	2(0.7)	1(2)
Rhinitis	3(0.99)	0
Cough	12(3.96)	0
Breathlessness	3(0.99)	0
Headache	3(0.99)	0
Myalgia	4(1.3)	0
Anosmia	1(0.3)	0
Diarrhea	1(0.3)3)	0
USG abnormalities, n (%)		
Polyhydramnios	5(1.7)	1 (2)
IUGR	1(0.3)	4 (8)
Positive for SARS-CoV-2 infection at delivery, n (%)		
Yes	206 (68)	30 (60)
No	97 (32)	20 (40)
Delivery day of mothers after becoming negative, n (%)		
< 7 days	55(18.2)	15 (30)
7-14 days	25(8.3)	5 (10)
PROM, n (%)	30(9.9)	4 (8)
Mode of delivery, n (%)		
Vaginal delivery	82 (27.1)	20 (40)
LSCS	221 (73)	30 (60)

IUGR=intrauterine growth restriction; PROM=premature rupture of membranes; LSCS=lower segment cesarean section

Table 2. Characteristics of SARS-CoV-2-infected and non-infected neonates

Neonatal characteristics	Infected neonates (n=50)	Non-infected neonates (n=309)
Sex, n (%)		
Male	24 (48)	173(56)
Female	26 (52)	136(44)
Mean gestational age (SD), weeks + days	38 + 6 (1 + 1)	38+3(1+5)
Mean birth weight (SD), g	3,070 (0.41)	2897(0.50)
Fetal distress, n (%)	3 (6)	53(17.2)
Perinatal depression, n (%)	1 (2)	14(4.5)
SGA, n (%)	4 (8)	35(11.3)
Preterm, n (%)	2 (4)	42(13.6)
Breastfeeding, n (%)	49 (98)	260(84.1)
Feed intolerance, n (%)	2 (4)	4(1.3)
Transient tachypnea of newborn, n (%)	2 (4)	13(4.2)
Phototherapy, n (%)	1 (2)	15(4.8)
Neonatal seizures on day 15, n (%)	1 (2)	0

SGA=small for gestational age

in neonates. Only 1 neonate had possible post-natal infection, since positivity was detected on day 5 of life and the caretaker was also positive for SARS-CoV-2.

A previous study reported that most pregnant women acquired COVID-19 infection in the third trimester, and COVID-19 was usually associated with a higher rate of CS, low APGAR indices, preterm births, and low birth weights.[12] The majority of mothers in our study were also infected in the third trimester. Similarly, CS rates were high in our study (71.1%), similar to studies in Mumbai (83.3%)6 and Turkey (71.2%).[9] Being a tertiary care hospital, most of the antenatal mothers were high-risk patients referred from peripheral hospitals, which may have been the reason for our high CS rate. The WHO reported that neonatal rates of SARS-CoV-2 infection do not appear to be affected by mode of delivery,[13] which was substantiated by the proportion of SARS-CoV-2-infected neonates delivered by CS in our study (60%). In addition, 12.3% of babies in this study were born preterm without much increase in preterm birth rate (2%) in positive neonates. The rate of IUGR in SARS-CoV-2-infected mothers was low in our study (5; 1.4%), of whom 4 were infected.

A review of 13 articles revealed that COVID-19 in mothers can cause fetal distress.[14] We also noted fetal distress in 56 neonates, of whom 7.1% were infected at birth. Fifteen neonates had low APGAR at 1 minute, of whom only 1 had SARS-CoV-2 infection and responded to tactile stimulation. The male to female ratio was 1.2:1 in another study,6 but females predominated slightly over males among positive neonates, with a ratio of 1.08:1.

Only 3% of positive neonates had mothers who were symptomatic, suggesting that maternal symptoms are poor predictors of infection in neonates. Another study in India of 7 infected neonates reported that 85.7% had symptomatic mothers, but the cohort was too small to predict risk of infection in newborns.8

While SARS-CoV-2-positive neonates in another study had respiratory and GI symptoms, as well as fever and severe disease,[11] the majority of our positive neonates were asymptomatic. Only 4 babies had mild symptoms of respiratory distress and feed intolerance, which was in agreement with another Indian study.6

Evidence for disease transmission through breastfeeding has been inconclusive.[12] Mother-infant pairs in our study roomed in and breastfed in 75% of at-risk neonates and 98% of positive neonates, after proper counseling regarding breast hygiene, hand hygiene, and droplet precautions. The follow-up testing at 5 days in the negative neonates and at 10 days in the cohort of positive neonates did not reveal any horizontal transmission, which was similar to a study in New York.[15] This finding suggests that risk of transmission from breastfeeding mothers can be reduced if proper precautions are followed.

The limitations of our study were that we did not test cord blood, placenta, or amniotic fluid specimens that would suggest vertical transmission, even though neonatal swab tests were done within 24 hours of birth. Moreover, a larger sample size of positive neonates would have been needed to predict risk factors for vertical transmission. Another limitation was that we could not follow up on neonates negative for SARS-CoV-2 infection beyond 5 days, which was needed to further detect any horizontal transmission.

The positivity test rate of SARS-CoV-2-infected neonates detected within 24 hours of birth indicates a high probability of congenital infection, either through vertical transmission. Maternal symptoms and SARS-CoV-2 infection at the time of delivery do not appear to increase the risk of infection in neonates. The majority of infected neonates were asymptomatic or had mild symptoms. Rooming-in and breastfeeding did not increase the risk of horizontal infection, when proper hygiene measures were followed.

Conflict of Interest

None declared.

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