Vertical transmission and clinical outcome of the neonates born to SARS-CoV-2-positive mothers: a tertiary care hospital-based observational study

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ABSTRACT

Background Neonatal transmission of SARS-CoV-2 from positive mothers to their babies has been a real concern, opening the arena of research in this area.

Objective To detect the possibility of vertical transmission of SARS-CoV-2 from COVID-19-positive mothers to their neonates and the clinicopathological outcome in them.

Design A single-centre, prospective, observational study involving 47 COVID-19-positive mothers and their neonates.

Setting A tertiary care hospital in Eastern India.

Participants Neonates born to SARS-CoV-2-infected mothers.

Main outcome measures We investigated the SARS-CoV-2 positivity rate by real-time reverse transcriptase-PCR (RT-PCR) done twice (on admission and after 24 hours of admission) in neonates born to SARS-CoV-2-positive mothers, who tested RT-PCR positive for this virus in their nasopharyngeal swab. Clinical outcome was also assessed in these neonates during their hospital stay.

Results Out of 47 neonates born to SARS-CoV-2-positive mothers, four were SARS-CoV-2 positive by RT-PCR. All the neonates in our study were discharged home in stable condition after management of acute complications. None of them required readmission.

Conclusion Vertical transmission occurs in neonates born to COVID-19-positive mothers; however, the risk is small. Majority of the neonates remain asymptomatic with good clinical outcome.

INTRODUCTION

COVID-19 infection first came to notice in Wuhan city in early December 2019. The most common manifestations consist of fever, cough, dyspnoea, malaise, fatigue and sputum secretion.¹ Additionally, infection with SARS-CoV-2 is not restricted to the respiratory system, but can trigger an excessive immune response, leading to multiple organ failure and death.² When compared with other coronaviruses causing diseases, the potential for transmission of SARS-CoV-2 is much higher.³ This is a cause for concern for vertical

What is known about the subject?

- Vertical transmission of SARS-CoV-2 is uncommon in neonates.

What this study adds?

- Vertical transmission does occur in neonates born to COVID-19-positive mothers, but the risk is small.

transmission from infected mothers to their newborn babies. Literature in this regard is limited, and exists both for and against the hypothesis. Initial reports from China seemed to suggest that vertical transmission did not take place.^{4–6}

Chen *et al* reported three women with confirmed COVID-19 infection where no viral nucleic acid was detected in the placentas or neonatal throat swabs by real-time reverse transcriptase-PCR (RT-PCR).⁴ Chen *et al* did a retrospective analysis of clinical records of nine pregnant women with confirmed COVID-19. No virus was detected from cord blood, amniotic fluid, throat swabs and breast milk.⁵ Zhang *et al* also did a retrospective study and evaluated the effect of COVID-19 on pregnancy outcome and neonatal prognosis between infected and non-infected women with COVID-19. No significant difference was found in neonatal outcome between the two groups. None of the neonates born to COVID-19-positive mothers tested positive for the virus.⁶ Case series of 116 patients from China has also reported no vertical transmission of COVID-19 to the neonates.⁷ Twenty-one neonates born to mothers with confirmed COVID-19 infection from New York were also assessed using RT-PCR test, 100% of the neonates tested negative.⁸

However, novel information continues to emerge that points towards possibility of vertical transmission. Alzamora *et al* reported a SARS-CoV-2-positive pregnant woman from Peru. The neonate, on delivery, was isolated immediately without delayed cord clamping or skin-to-skin contact. The neonate tested positive for SARS-CoV-2 at 16 hours after delivery.⁹ Vivanti *et al* described a case of congenital infection associated with neurological manifestation. The placental tissue as well as the neonatal blood tested positive for SARS-CoV-2, suggesting transmission through the placenta.¹⁰ Early-onset infection with neurological manifestation has also been described from Germany in a neonate whose mother presented for delivery with fever and loss of sense of taste and smell. The neonate was immediately isolated but developed progressive encephalitic symptoms and tested positive for SARS-CoV-2.¹¹ Dong *et al* reported an infant with elevated SARS-CoV-2 IgM antibody and cytokine levels born to a mother with confirmed COVID-19 infection.¹² Zamaniyan *et al* described a pregnant woman with severe COVID-19 pneumonia who delivered a healthy preterm baby. The amniotic fluid as well as the neonate tested positive for COVID-19, suggesting infection was acquired during intrauterine period.¹³ The literature review done by Shalish *et al*¹⁴ which included 217 neonates from across 27 publications found four neonates to be positive for SARS-CoV-2 (1.8%). All of them had favourable clinical outcomes. Thus, although small, the risk of vertical transmission does exist. A cohort study of 33 infants by Zeng *et al* also provides evidence that likely source of SARS-CoV-2 infection could be maternal in origin.¹⁵ A large study in the UK including 265 neonates born to COVID-19-positive mothers found 5% positivity (12/265).¹⁶ In contrast, analysis of data from the National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection found 44/2287 (1.9%) of the neonates born to mothers with confirmed COVID-19 infection to be positive.¹⁷ Zhu *et al*'s retrospective analysis of outcomes of 10 infants born to COVID-19-positive mothers concluded that adverse events including death were possible in perinatally acquired SARS-CoV-2 infection.¹⁸ More reports of adverse pregnancy outcome have come forth. Baud *et al* reported a patient positive for SARS-CoV-2 who delivered a stillborn infant. Swabs from the fetal side of the placenta were positive for SARS-CoV-2.¹⁹ Another case report described preterm delivery in a COVID-19-positive mother. RT-PCR test of placental and umbilical cord samples was positive for SARS-CoV-2 RNA.²⁰ Preterm delivery has been found to be the most common adverse outcome.^{8 21} A systematic review and meta-analysis by Kotlyar *et al* has concluded that vertical transmission of SARS-CoV-2 does occur in a minority of cases. This positivity was found to be similar to pathogens causing other congenital infections. Highest positivity was from rectal swabs (9.7%), then placental samples (7.7%), followed by nasopharyngeal swab (NPS) (3.2%).²²

Given the still incomplete understanding of the COVID-19 virus and its effect on different vulnerable

population, information about how this disease behaves is still evolving. Our study aims to objectively assess whether vertical transmission of SARS-CoV-2 occurs, and if it does, then to assess the severity of illness it can induce.

METHODS

Study participants

Neonates born to COVID-19-positive mothers between July and December 2020.

Study settings

The study was conducted at a tertiary care hospital in Eastern India. Our hospital was providing services as a 'dedicated COVID-19 hospital' from June 2020 to January 2021 during the first wave of the SARS-CoV-2 pandemic in India.

Study design

This was a hospital-based prospective observational study to determine whether vertical transmission of SARS-CoV-2 occurs, and if it does then to assess the clinical presentation, disease course and outcome of these newborns. Informed consent for participation in the study was taken from expectant mothers coming for delivery who tested positive for viral RNA in their NPS by RT-PCR at the time of hospital admission. Since our hospital was a COVID-19-dedicated centre during the study period, we only admitted patients who were positive for COVID-19. Neonates were investigated by taking two NPS, one within 24 hours of delivery, and second 24 hours after the first test. Neonates testing positive in either of the two samples were considered positive. Neonates, on delivery, were immediately transferred to a designated newborn nursery and kept there for monitoring of symptoms, until their NPS samples were processed for the presence of SARS-CoV-2 and they were fit to discharge to home. Newborns were fed with expressed breast milk, and if unavailable or inadequate, then supplemented with formula feeds. Mothers were discharged as per institutional protocol. Symptomatic as well as asymptomatic mothers were advised to isolate at home for the next 14 days after discharge, they were encouraged to breast feed their newborns with masks covering their nose and mouth. Neonates were discharged with advice of (a) breast feeding, (b) mother to maintain hand hygiene and use of face masks while breast feeding, and (c) infant's cot or resting to be separated from the mother's bed by at least 1.5–2 m. Danger signs indicating sickness in the newborn were explained and mothers were given a child helpline number to contact in case of appearance of any of the danger signs. Additionally, they were advised for routine follow-up for immunisation at 6 weeks of age.

Qualitative RT-PCR

Real-time RT-PCR was done by using one-step real-time PCR reaction mixture and primer-probe mixture which was approved by the Indian Council of Medical Research,

Government of India. All of the real-time PCR kits used were able to amplify at least one screening and one confirmatory gene. In addition, primer-probe detecting an internal control gene (human RNase P) was also included in all the samples. The samples were run along with positive control and a no template control for validation of the run. Real-time RT-PCR was performed in either Bio-Rad CFX96 or ABI QuantStudio 5 Dx machine with reaction protocol set as per instruction from the kit manufacturer.

Statistical analysis plan

The continuous data were tested for normal distribution using the one-sample Shapiro-Wilk test. Further, the continuous data were presented as mean $\pm$ SD or median (IQR) based on the nature of their distribution. All statistical analyses were performed with STATA V.13 software (StataCorp, Texas, USA).

Patient and public involvement

Patient and/or the public were not involved in the design, or recruitment, or conduct, or reporting, or dissemination of plans of the study.

RESULTS

A total of 47 COVID-19-positive mothers and their neonates were included in the study. Majority of them were asymptomatic (41) whereas 4 mothers had mild symptoms, 1 mother had moderate symptoms and 1 mother had presented with severe acute respiratory infection (SARI) (table 1). More than half of the mothers²³ did not have any obstetric complications. More than half of the mothers²³ underwent emergency lower section caesarean section (LSCS) whereas 14 had elective LSCS and only eight had normal vaginal delivery. Previous LSCS and fetal distress were the most common indications for LSCS (table 2). Of the 47 neonates, 25 were female and 22 were male, out of which 2 males and 2 females were COVID-19 positive. The mean weight of the neonates was 2.7 $\pm$ 4.2 kg. Most of our neonates were born at term gestation (40/47), and all COVID-19-positive newborns were term babies. Six were preterm and one was born post-term. Majority of the neonates had normal birth weight (30); however, 16 neonates had a low birth weight, and one neonate had a very low birth weight (table 3). All COVID-19-positive newborns had normal birth weight. We found that majority of neonates (44) born to COVID-19-positive mothers were asymptomatic at birth, while only two neonates suffered from symptoms. One neonate had abdominal distension and respiratory distress (RD) from the first few hours of life. The baby was negative for COVID-19 on tests taken both on the day of admission and 24 hours later, but found to have elevated lactate dehydrogenase (LDH) (1685.7 IU/L), D dimer (>20 mcg/mL) and serum ferritin (259.6 ng/mL). C-reactive protein (CRP), absolute neutrophil count (ANC) and platelet count were within normal limits. She was

Table 1 Baseline characteristics of COVID-19-positive mothers

Characteristics	Mean $\pm$ SD
Gestation (weeks)	37.6 $\pm$ 1.8
COVID-19 classification of mother	
Asymptomatic	41
Mild	4
Moderate	1
SARI	1
Obstetric complications	
None	25
Diabetes mellitus	2
GDM	7
Hypertension	4
Pre-eclampsia	1
Hypothyroidism	4
Tuberculosis	1
IHCP	2
Portal vein thrombosis	1

GDM, gestational diabetes mellitus; IHCP, intrahepatic cholestasis of pregnancy; SARI, severe acute respiratory infection.

discharged in stable condition after 5 days of admission. The second neonate also had RD and recurrent vomiting from day 1 of life. This term neonate also did not test positive for COVID-19 on either of the two tests, but had elevated LDH (727.2 IU/L), D dimer (3.1 mcg/mL) and serum ferritin (414.6 ng/mL) with normal levels of CRP, ANC and platelet count. She was also discharged in stable condition.

Two consecutive RT-PCR testings of each neonate were done, first on the day of birth and the second one 24 hours later. In the first RT-PCR test, only one neonate tested positive, whereas in the second RT-PCR test three

Table 2 Mode of delivery and outcomes in COVID-19-positive mothers

Characteristics	n
Mode of delivery	
NVD	8
Elective LSCS	14
Emergency LSCS	25
Indication of LSCS	
Fetal distress	13
MSL	6
Placenta previa	3
Previous LSCS	16
Obstructed labour	1

LSCS, lower section caesarean section; MSL, meconium-stained liquor; NVD, normal vaginal delivery.

Table 3 Baseline characteristics of the neonates

Characteristics	COVID-19 status, n	
	COVID-19 negative	COVID-19 positive
Gender		
Female	23	2
Male	20	2
Gestation		
Term	36	4
Preterm	6	0
Post-term	1	0
Birth weight (g)		
Mean±SD	2776.7±426.4	
Very LBW	1	0
LBW	16	0
Normal birth weight	26	4
EBM/formula feeds		
EBM	1	
FF	6	
Both	35	
Symptomatic status of neonate		
Asymptomatic	40	4
Symptomatic	2	0

EBM, expressed breast milk; FF, formula feeds; LBW, low birth weight.

other neonates tested COVID-19 positive. Few neonates developed complications after the first 24 hours of life, for example, shock; or had a more plausible alternate explanation, for example, birth asphyxia and transient tachypnoea of newborns (table 4). Among the four COVID-19-positive neonates, none experienced any neurological (CNS), respiratory, gastrointestinal (GIT) and cardiovascular (CVS) complications. All the neonates included in the study survived and were discharged in stable condition. Sepsis screen was negative for all neonates.

DISCUSSION

The potential for vertical transmission of SARS-CoV-2 has been an area of much debate and concern. Initially, most of the information on this topic came from small case series and isolated case reports.⁴⁻⁶ Additionally, majority of these data were from China, the country where the pandemic was first detected, and North America.⁸ Large population-based data are still lacking from diverse population like South East Asia. In our study, we had four out of 47 neonates who tested positive for COVID-19 from RT-PCR of their NPS. This is in contrast to the study done in New York where all 21 neonates born to confirmed COVID-19-positive mothers tested negative,⁸ and also goes against evidence from China carried out by Chen *et*

Table 4 Neonatal complications

Complication	COVID-19 status, n	
	COVID-19 negative	COVID-19 positive
CNS		
Birth asphyxia	2	0
ICH	1	0
Respiratory		
TTNB	2	0
RDS	0	0
Pneumonia	1	0
MAS	1	0
Apnoea	0	0
GIT		
Feed intolerance	2	0
NEC	0	0
Cardiovascular		
CHF	0	0
Myocarditis	0	0
Shock	1	0
CHD	0	0
Metabolic		
NNH	8	1
Dyselectrolytaemia	3	0
Hypoglycaemia	5	1
Treatment		
Antibiotics	3	1
Intravenous fluids	5	0
Inotropes	1	0
Outcome		
Discharge	43	4

CHD, congenital heart disease; CHF, congestive heart failure; CNS, central nervous system; GIT, gastro-intestinal tract; ICH, intracranial haemorrhage; MAS, meconium aspiration syndrome; NEC, necrotising enterocolitis; NNH, neonatal hyperbilirubinaemia; RDS, respiratory distress syndrome; TTNB, transient tachypnoea of newborn.

*al*⁵ and Zhang *et al*.⁶ However, these studies were carried out on less than half the number of patients than our study. Zeng *et al*'s study with the patient cohort similar to ours was in favour of maternal vertical transmission.¹⁵ Moreover, larger studies from the UK¹⁶ and several publications from around the globe¹⁴ also favour that vertical transmission is indeed possible. Immediate skin-to-skin contacts with mothers or delayed cord clamping was not allowed. All neonates were immediately isolated in a designated neonatal unit. Their NPS for RT-PCR were sent immediately following delivery. Neonates were handled by staffs in personal protection kit (PPE) and they worked in alternate week shifts followed by a week of quarantine, followed by mandatory COVID-19 RT-PCR

test from NPS and a negative report before joining the duty. Despite our best precautions against airborne, droplet and contact transmission, however, it is difficult to say whether the three newborns who tested positive after 24 hours of life did not acquire infection from the environment or an asymptomatic caregiver. Plausible explanation for second NPS being positive could be a viral load which was insufficient initially for detection, but due to viral replication the viral load became detectable after 24 hours of life. A single negative test does not often exclude the diagnosis particularly in endemic areas.²⁴ Most of our newborns were fed using expressed breast milk, supplemented with formula, but emerging evidence has pointed against transmission of SARS-CoV-2 through breast milk.^{23 25 26} Isolated case reports describing mothers with severe infection who delivered positive neonates,⁹ as well as mothers with mild or no infection having delivered positive newborns,^{11 12} exist. All four newborns that tested positive in our study had asymptomatic mothers. One mother in our study had COVID-19-induced SARI, and one was classified as moderate according to the WHO disease classification,²⁷ but both of their newborns tested negative for COVID-19. Adverse events like fetal distress and prematurity are among the most common pregnancy outcomes described in SARS-CoV-2.^{18 21} Fetal distress was the most common obstetric complication in our study (13/47). Since we did not test the amniotic fluid or placental tissue for evidence of SARS-CoV-2 virus, it is difficult to tell whether these newborns had complications related to COVID-19 virus transmitted vertically from the mother or not. Intervillous inflammation on placental pathology has been found in confirmed cases,^{10 19} even where fetal swabs have tested negative.¹⁹ Therefore, the possibility of SARS-CoV-2-induced complications in neonates of confirmed cases cannot be ruled out solely on the basis of negative RT-PCR from NPS, where simultaneous evaluation of placental tissue and amniotic fluid has not been carried out.²⁰ Several case series and some systematic reviews have also pointed towards preterm delivery as the most common adverse clinical outcome.^{8 21} Most of the newborns in our study were term babies, and only six out of 47 were born preterm. All COVID-19-positive newborns were delivered at term gestation. We only tested NPS samples of neonates and found four out of 47 neonates to be positive. This is similar to the positivity found by Kotlyar *et al.*²²

All the neonates were discharged in stable condition and none required readmission. Our study favours the view that vertical transmission does occur in neonates born to COVID-19-positive mothers; however, the risk is small. Majority of them remain asymptomatic with good clinical outcome.

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Contributors PK conceptualised this research. AA was involved in initial drafting of the protocol with PK. F and PK were involved in collecting data and drafting of

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Competing interests None declared.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information. Data are available on reasonable request. All relevant data are available on reasonable request by emailing the corresponding author.

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