Journal of Paediatrics and Child Health

doi:10.1111/jpc.15989

ORIGINAL ARTICLE

Clinical manifestations of SARS-CoV-2 infection in neonates and the probability of maternal transmission

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Aim: This study aimed to measure the incidence of SARS-CoV-2 infection in neonates from infected mothers and to screen disease severity in neonates.

Methods: We conducted a population-based cohort study of neonates from SARS-CoV-2-positive mothers, enrolling mothers who tested positive for SARS-CoV-2 and their neonates. Eleven infants <25 days old presenting with SARS-CoV-2 infection were also included in the study. We recorded clinical symptoms of SARS-CoV-2-positive mothers and their neonates.

Results: One of 126 babies born to SARS-CoV-2-infected mothers was found to be positive (0.79%). The referred positive neonates were either asymptomatic or suffered from symptoms ranging from mild respiratory distress to pneumonia. Most SARS-CoV-2-positive neonates showed neutropenia and lymphocytosis. Most of the SARS-CoV-2-infected mothers ($n = 126$) were either asymptomatic (46, 36.5%) or showed mild respiratory distress (66, 52.4%). However, pneumonia and severe respiratory distress were reported in 14 (11.1%) of the SARS-CoV-2-infected mothers. There were no deaths of either SARS-CoV-2-infected mothers or neonates.

Conclusion: We conclude that mothers transmitted infection to their neonates at a very low rate. Disease in neonates is usually mild, although some babies have severe disease. SARS-CoV-2 infection in late pregnancy usually leads to mild maternal disease, but severe disease is reported in approximately one-tenth of the infected women.

Key words: COVID-19; maternal infection; neonatal infection; SARS-CoV-2.

What is already known on this topic

1 Maternal to neonatal transmission of SARS-CoV-2 infection is rare; however, reports vary greatly in reporting its incidence.
2 The severity of SARS-CoV-2 infection is similar in pregnant and non-pregnant women.
3 Studies report varying severity of disease due to SARS-CoV-2 infection in neonates.

What this paper adds

1 We found that mothers transmitted SARS-CoV-2 infection to their neonates at a low rate (1/126).
2 Disease in neonates was usually mild, but severe disease was reported in 16.6% (2/12) of infected babies.
3 SARS-CoV-2 infection in late pregnancy usually leads to mild disease, but severe disease was reported in 11.1% (14/126) of infected women.

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a newly emerged coronavirus that was initially identified in China in December 2019. Globally, COVID-19 has been confirmed in approximately 497 million cases, with more than 6 million deaths reported to the World Health Organization as of 12 April 2022.[1] The virus is related to the subgenus *Sarbecovirus*, genus *Betacoronavirus*, within the family *Coronaviridae*. Angiotensin-converting enzyme-2 (ACE-2) is the cell receptor used by the virus to enter cells.[2]

The virus is highly transmissible among people through both direct and indirect contacts. Respiratory droplets or aerosols can transmit infection directly, while contaminated objects and surfaces can also play a role in virus transmission among people through indirect contact.[3] SARS-CoV-2 has an incubation period of 5–7 days; however, it can take up to 14 days to develop symptoms after being exposed to the virus.[4] SARS-CoV-2 shedding occurs 1–3 days before the onset of disease symptoms and reaches its peak within the first 3 days after the appearance of clinical symptoms.[5,6] Asymptomatic cases can constitute a potential source of infection to other people.[5] In symptomatic patients, the period of infectious viral shedding is 8 days from the onset of clinical symptoms.[7] Up to 20% of patients who become symptomatic develop severe disease that necessitates the use of oxygen, and some develop life-threatening disease with respiratory and/or multiorgan failure.[8]

Compared to non-pregnant women of reproductive age, pregnant women with COVID-19 appear to be less likely to be symptomatic or display common symptoms, such as fever, dyspnea and myalgia.[9] Severe COVID-19 is associated with maternal age,

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Conflict of interest: None declared.

Accepted for publication 7 April 2022.

a high body mass index, pre-existing comorbidities, chronic hypertension and pre-existing diabetes.[9]

Although there are some published data about the neonatal infections of SARS-CoV-2, wide variations do exist in different reports regarding disease severity and the probability of transmission of SARS-CoV-2 infection from the mothers to their babies, and most of the data are obtained from case reports.[10–13] Race was also found to affect the severity of neonatal infection by SARS-CoV-2 as Asian or Black ethnicity suffered from more severe disease than other ethnic groups.[13] The current study aims to screen the possibility of neonatal infection from laboratory-confirmed pregnant women, as well as disease severity in both babies and their mothers.

Methods

Ethical approval

The study was approved by the Research Ethics Committee, Directorate of Health Affairs – Taif (IRB registration number HAP-02-T-067; approval number 353).

Study design and procedures

A population-based cohort study was conducted. The data of the SARS-CoV-2-positive mothers ($n = 126$) and their respective newborn babies were collected from 6 April 2020 to 15 July 2021 in the King Faisal Medical Centre, Taif, Saudi Arabia. The study also included newborns who showed laboratory-confirmed SARS-CoV-2 results after delivery due to contact with infected family members ($n = 11$). The throat swabs from patients were screened using the Abbott's molecular point-of-care platform ID NOW COVID-19 kit (Abbott, Scarborough Diagnostics, ME, USA) that targets a unique region of the RNA-dependent RNA polymerase (RdRp) of the SARS-CoV-2. The test is based on an isothermal amplification using fluorescent-labelled molecular beacons. The national policy recommended routine assessment of neonates from SARS-CoV-2-positive mothers every 3 days. They were required to have two negative results before being discharged from the hospital. In addition, the clinical symptoms of the mothers and their neonates, neonatal management and outcomes were reported.

Laboratory investigations

Haematological investigation, including total and differential blood counts, renal function tests (urea and creatinine) and liver function tests, including glutamate-oxaloacetate transaminase and glutamate pyruvate transaminase and bilirubin, was conducted on infected babies according to the manufacturer's instructions.

Outcomes and definitions

This analysis presents the characteristics and outcomes for babies detected positive for SARS-CoV-2 infection before 30 days of age. Cases that showed at least two of the following were considered severe or critical, as previously described[14]: (i) any of fever (>37·5°C), apnoea, cough, respiratory distress tachypnoea, chest recession, supplemental oxygen requirement, poor feeding or vomiting or diarrhoea; (ii) any of low white blood cell count ($<5 \times 10^9$/L) or low lymphocyte count ($<1 \times 10^9$/L) and (iii) abnormal chest X-ray and probable or possible neonatal intrapartum acquired infection, as previously described.[15]

Statistical analysis

Descriptive statistics are presented as frequencies, percentages were estimated and χ^2 values were calculated using SPSS Statistics for Windows, Version 16.0 (Armonk, IBM, Corp, NY, USA).

Results

All mothers ($n = 126$) were either admitted to the hospital as SARS-CoV-2-positive patients or suspected patients who were confirmed to be positive 24 h after admission. The age of the pregnant women ranged from 22 to 44 years, and their mean age was 28.6 ± 0.45 years (Table 1). Except for a single case of pre-eclampsia, none of the patients suffered from any chronic disease. The clinical symptoms of pregnant women who were detected as SARS-CoV-2 positive ($n = 126$), as well as their respective neonates, were examined through ID NOW COVID-19 assay over the study period. Babies from confirmed SARS-CoV-2-positive mothers were screened for the infection through ID NOW COVID-19 assay 24 h after delivery. The neonates were directly separated from suspected or positive mothers after birth in an isolated neonatal intensive care unit (NICU).

In the current study, 46 (36.5%) of 126 SARS-CoV-2-infected mothers were asymptomatic, 66 (52.4%) of 126 had mild respiratory distress, 1 had diarrhoea, 1 had vomiting and abdominal distension and 14 (11.1%) of 126 showed severe pneumonia (Table 1).

Eleven additional babies were admitted and referred from other hospitals and confirmed to be SARS-CoV-2-positive. These babies aged 18–27 days. They become infected due to post-natal infections transmitted from their mothers or other family

Table 1 Clinical characteristics of SARS-CoV-2-positive pregnant women

Item	Number
Mean age (range)	28.6 ± 0.45 [22–44 years]
Delivery	
Normal delivery	47 (37.3%)
Caesarean section	79 (62.7%)
ICU	14 (11.1%)†
Not in ICU	112 (88.9%)
Asymptomatic	46 (36.5%)
Mild respiratory distress	66 (52.4%)
Diarrhoea	1 (0.8%)
Vomiting and abdominal distension	1 (0.8%)
Pre-eclampsia	1 (0.8%)
Premature rupture of the fetal membranes	1 (0.8%)
Mortality	0 (0.0%)

† Pneumonia, oxygen therapy. ICU, intensive care unit.

Table 2 COVID-19 clinical signs in SARS-CoV-2 laboratory confirmed positive babies

Affected cases	Gender	Age (days)	Number of SARS-CoV-2-positive samples	Signs
Case 1	Girl	9	4	None
Case 2	Boy	18	3	None
Case 3	Boy	13	7	Mild respiratory distress
Case 4	Girl	16	10	Mild respiratory distress and dermatitis
Case 5	Girl	18	7	Fever for 10 days
Case 6	Girl	22	9	Fever for 1 day, severe cough
Case 7	Boy	24	14	Fever for 1 day
Case 8	Boy	6	1	Mild respiratory distress
Case 9	Girl	21	1	Cough
Case 10†	Girl	1	7	Pneumonia and abnormal chest X-ray
Case 11	Boy	27	7	Fever for 2 days
Case 12	Boy	20	5	Pneumonia and abnormal chest X-ray

† 2510 g, normal birth at 37 weeks. A non-significant χ^2 (0.255) value was detected among different cases with respect to disease severity and persistence of the virus, as indicated by the number of positive SARS-CoV-2 results. All cases were full-term, and their mothers were not admitted to the ICU. SARS-CoV-2 was screened using ID NOW COVID-19 assay.

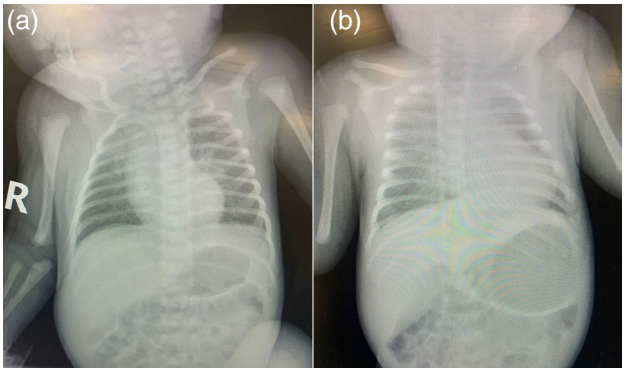

Fig. 1 Chest X-ray of babies suffering from pneumonia. (a) Anterior–posterior view of chest X-ray of 1-day-old baby (case 10) shows bilateral diffuse pulmonary infiltrates and ground glass appearance with normal size heart shadow. (b) Anterior–posterior view of chest X-ray of 20-day-old baby (case 12) shows bilateral diffuse ground glass appearance with localised area on the right upper-lung lobe of dense infiltration with normal heart and bone shadow.

members. One out of the 126 eligible neonates born from SARS-CoV-2-infected mothers tested positive for SARS-CoV-2 (case 10). This baby showed severe respiratory distress and was intubated. The mother of case 10, suffered from respiratory distress, was subjected to normal spontaneous vaginal delivery and gave birth to a full-term girl (37 weeks). The rest of the babies were transferred from other hospitals after testing positive for the virus. Two of the babies showed no clinical signs, 3 of 12 babies showed fever as the only clinical sign, 3 of 12 babies showed mild respiratory distress, 2 of 12 babies suffered from cough and 2 of 12 babies suffered from pneumonia and severe respiratory distress (Table 2, Fig. 1). All cases were subjected to ID SARS-CoV-2 screening every 72 h until they showed two consecutive negative results. There was no correlation between disease severity in the babies and the duration of being positive. One baby showed 14 positive results (case 7) and developed fever for 1 day only. Another baby suffered only from mild respiratory signs and showed 10 positive COVID-19 results. A third baby showed nine positive results and suffered from severe cough. The two babies who suffered from pneumonia (cases 10 and 12) showed positive results for 7 and 5 consecutive samples, respectively (Table 2). Although the total white blood cell (WBC) count was within the normal range in all babies, relative neutropenia was detected in 8 of 12 babies. Eosinophilia was detected in a single neonate (case 7). This was not related to COVID-19 infection but a protozoal infection that was confirmed by improvement following treatment with metronidazole. Both renal and liver function tests were found normal; however, a single case showed high bilirubin, which is not related to COVID-19 but physiological jaundice (Table 3).

Discussion

In the current study, 14 (11.1%) of 126 mothers were suffered from severe pneumonia without any fatal consequences. The results of the current study agree with those of the other studies that reported severe COVID-19 infection in 9.9–12.8% of the infected patients.[16,17] Both SARS-CoV and MERS-CoV are considered to induce severe disease symptoms with fatal consequences in pregnant women.[18,19] This finding agrees with the other findings, which confirmed that disease severity in pregnant women does not significantly differ from that in non-pregnant women.[12,13,20] In a study from China, among 116 COVID-19-infected pregnant women, only 8 (6.9%) showed severe pneumonia without any fatal consequences.[12] In addition, fewer adverse maternal effects have recently been recorded in COVID-19-infected mothers in the United Kingdom.[13] In a case series from Iran, a high mortality rate was reported following SARS-CoV-2 infection in nine pregnant women.[21] In contrast, the current study reported asymptomatic infections in 46 (36.5%) of the infected mothers. This finding agrees with those of the previous

Table 3 Haematological and biochemical analysis of COVID-19-positive babies

Item	Case number											
	1	2	3	4	5	6	7	8	9	10	11	12
WBC (K/μL)	7.7	14.73	12.98	6.73	16.15	7.73	12.67	9.23	7.28	12.43	8.81	16.6
RBC (M/μL)	3.54	4.06	4.12	3.98	3.17	3.35	4.44	4.42	4.17	3.5	3.82	3.98
Hb (g/dL)	10.7	11.7	12.8	11.2	10.8	10.7	16.1	15.7	11.8	10.9	11.1	13.8
Haematocrit (%)	33.6	38	37.4	33.6	32.1	32	53.3	46.6	35.3	33.5	32.9	39.1
Platelets (K/μL)	512	664	306	658	340	322	332	442	253	330	614	495
Neutrophils (K/μL)	1.16	1.46	1.7	0.8	7.37	1.34	3.72	3.27	1.89	0.39	0.89	4.17
Neutrophils (%)	15.1	10	13.1	11.9	45.8	17.3	29.4	35.4	26	3.2	10.1	25
Lymphocyte (K/μL)	5.37	11.26	10.2	11.9	6.92	5.71	5.69	3.52	4.13	10.72	7.09	10.8
Lymphocytes (%)	69.7	76.4	78.6	77.4	42.8	73.9	44.9	38.1	56.7	86.2	80.5	64.9
Monocytes (K/μL)	0.79	1.3	1.03	5.2	1.62	0.51	1.79	1.76	1	1.06	0.54	1.3
Monocytes (%)	10.3	8.8	7.9	6.1	10	6.6	14.1	19.1	13.7	8.5	6.1	7.9
Eosinophils (K/μL)	0.03	0.64	0.01	0.28	0.2	0.16	1.39	0.58	0.24	0.25	0.28	0.33
Eosinophils (%)	4.5	4.3	0.1	4.2	1.2	2.1	11	6.3	3.3	2	3.2	2
Basophils (K/μL)	0.02	0.07	0.04	0.01	0.04	0.01	0.08	0.1	0.02	0.01	0.01	0.01
Basophils (%)	0.4	0.5	0.3	0.1	0.2	0.1	0.08	1.1	0.3	0.1	0.1	0.1
Blood urea (mg/dL)	26.1	21.2	16.2	22.5	11.6	9.8	22.3	5.5	25	19.3	5.6	10.4
Creatinine (mg/dL)	0.18	0.31	0.12	0.31	0.19	0.14	0.28	0.42	0.15	0.28	0.17	0.12
SGOT – AST	24	33	24	25	35	30	25	20	29	22	30	28
SGPT – ALT	9	19	15	12	19	25	19	6	15	18	16	17
Bilirubin total	0.669	0.427	0.462	0.482	0.325	0.535	1.535	8.606	2.971	0.242	0.453	1.611
Bilirubin direct	0.266	0.108	0.209	0.219	0.104	0.204	0.442	1.652	0.605	0.117	0.233	0.45

Abbreviation: ALT, alanine aminotransferase; AST, aspartate; HB, haemoglobin; RBC, red blood cell; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum Glutamic-oxaloacetic transaminase; WBC, white blood cell.

studies that reported asymptomatic infections in 20–50% of pregnant women.[10,22]

The current study reports the probability of SARS-CoV-2 infection from infected mothers to their respective neonates. All babies born from positive mothers were routinely examined for SARS-CoV-2 infection 24 h after birth. This fact cannot exclude vertical transmission or the possibility of catching the infection from other babies in the paediatric ICU unit or the NICU. However, the probability of spreading the infection from SARS-CoV-2-positive mothers to their respective babies was low, as only 1 of 126 patient tested positive. This finding agrees with that of another cohort, which suggested that SARS-CoV-2 neonatal infection does not occur even when neonates are breastfed by infected mothers.[10]

In contrast, the referred SARS-CoV-2-positive babies ($n = 11$) showed variable degrees of disease severity. Based on the criteria defined by Shah *et al*., only two babies showed severe COVID-19 disease.[15] This finding agrees with that of a recent study that reported high percentages of SARS-CoV-2-positive neonates suffering from mild disease.[23] In contrast, 42% (28/66) of neonates had severe neonatal SARS-CoV-2 infection[13] .

In our study, 100% of the infected babies were discharged without any further treatment compared to the value of 60% reported by Gale *et al*.[13] However, these authors related such deterioration to not only SARS-CoV-2 infection but also other reasons, including neonatal prematurity.[13]

In the current study, an asymptomatic infection was reported in two babies. However, it cannot be correlated to the maternal transfer of anti-SARS-CoV-2 antibodies from infected mothers to their neonates since the transfer of such antibodies is significantly impaired in patients infected in the third trimester.[24,25] Meanwhile, this could be explained by the amplitude of immune responses and the ACE-2 expression pattern.[26,27] The separation of neonates from their mothers is not recommended and has detrimental effects on both babies and their mothers.[28,29] However, in Saudi Arabia, prompt separation of neonates is adopted. Since the last 6 months, this has not been used in the current protocol adopted in the KSA.

There was a wide variation in the presence of SARS-CoV-2 RNA in infected babies, which ranged from 3 days to ≤42 days regardless of disease severity in the infected babies. Although not related to neonatal infection, our findings agree with those of a previous study that screened SARS-CoV-2 RNA in infected patients with a similar range of RNA detection in infected patients.[30]

Conclusion

The current study indicates a low probability of neonatal transmission of SARS-CoV-2. Neonatal and maternal infections usually result in mild-to-moderate disease manifestations; however, a serious infection does occur in a considerable number of patients.

The limitations of this study include a focus on essential data to limit the reporting burden on neonates; therefore, we did not collect detailed longitudinal data on physiological status or biochemical or haematological test results from mothers. In addition, we collected only the available data without specifying certain testing to be conducted. In addition, the genotype of the infected strains was not determined as disease severity could be correlated to the infected strain.

Acknowledgement

The authors acknowledge the support of the Taif University Researchers Supporting Project Number (TURSP-2020/11), Taif University, Taif, Saudi Arabia.

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