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Characteristics and outcomes of SARS-CoV-2 positivity in neonates born to mothers with COVID-19 in Klang Valley, Malaysia: a retrospective observational study

Sok Bee Lim [a,*], Kwee Ching See [a], Kian Boon Law [b], Nor Izwah Mohamed Kamarudin [a]

[a] Pediatric Department, Sungai Buloh Hospital, Ministry of Health Malaysia, Selangor, Malaysia
[b] Digital Health Research and Innovation Unit, Institute for Clinical Research, Ministry of Health Malaysia, Selangor, Malaysia

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ABSTRACT

Objective: The aim of this study was to analyze the clinical characteristics of neonates born to mothers with coronavirus disease 2019 (COVID-19), along with the incidence and outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positivity in Klang Valley, Malaysia.

Methods: The clinical records of all neonates born to mothers with COVID-19 who were admitted to Sungai Buloh Hospital, Selangor, Malaysia from October 1, 2020 to September 30, 2021 were reviewed retrospectively. Data collected included demographic details and the incidence, risk factors, and clinical outcomes of neonates with SARS-CoV-2 positivity.

Results: A total of 766 neonates from 753 mothers with COVID-19 were included. Overall, 23 (3%) neonates tested positive by nasopharyngeal swab SARS-CoV-2 PCR taken within the first 8 days of life. There were three (0.4%) confirmed and four (0.5%) probable neonatal infections acquired intrapartum, seven (0.9%) confirmed neonatal infections acquired postpartum, and nine (1.2%) cases that did not fit within the classification. The rate of preterm delivery was 25% among all neonates born to mothers with COVID-19 and 39.1% among SARS-CoV-2-positive neonates. Of the SARS-CoV-2-positive neonates, 43.5% required ventilatory support. Factors identified to have a significant association with neonate SARS-CoV-2 positivity included maternal antepartum hemorrhage (odds ratio (OR) 7.33, $P = 0.014$), place of delivery in a non-designated COVID-19 center (OR 7.64, $P < 0.001$), exposure to the mother post-delivery (OR 4.13, $P = 0.014$), and a higher 5-minute Apgar score (score 6–10; OR 0.20, $P = 0.0037$).

Conclusions: This study identified a risk of SARS-CoV-2 transmission from mothers with COVID-19 to their offspring, with infection acquired predominantly postpartum. A higher incidence of preterm delivery and ventilatory support were observed among SARS-CoV-2-positive neonates.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported among adults and children in late December 2019 in Wuhan, China. Within a few months, this infection had spread rapidly across the globe and was declared a pandemic by the World Health Organization (WHO) in March 2020 (World Health Organization 2020).

There has been increasing evidence of vertical transmission of SARS-CoV-2, as supported by a recent living systematic review and meta-analysis (Allotey et al., 2022). Vertical transmission was found to account for approximately 1.8% (range 0.1–5.7%) of the overall SARS-CoV-2 positivity rate among the offspring of mothers with COVID-19.

The aim of this study was to describe the characteristics and outcomes of SARS-CoV-2 positivity in neonates born to mothers with COVID-19 in Klang Valley, Malaysia.

COVID-19 was first reported in Malaysia on January 25, 2020. Since then, Malaysia has been hit with multiple waves of COVID-19. The first COVID-19 wave lasted from January 25 to February 16, 2020. The second wave occurred between February 27 and June 30, 2020. The third wave officially started on October 8, 2020, with the highest peak being over 22 262 daily positive cases, a hospitalization rate of 11%, and intensive care unit (ICU) admission rate of 6.8%. The fourth wave officially began on January 26, 2022. Although this fourth wave had a higher peak of 33 406 daily positive cases, these cases were relatively milder, with a hospitalization rate of 6.6%

* Pediatric Department, Hospital Sungai Buloh, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia
E-mail address: sokbee88@hotmail.com (S.B. Lim).

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and ICU admission rate of 1.1% (Rampal et al., 2021; COVID NOW, 2022).

From January 1, 2021 to August 9, 2021, there was an increasing trend of pregnant women with COVID-19 in Malaysia, with 70 recorded deaths due to COVID-19 complications as compared to zero maternal mortality in 2020. This prompted COVID-19 vaccination for pregnant women to be introduced nationwide in Malaysia in June 2021 (National Institutes of Health Malaysia, 2021). Therefore, the present study covered the period from October 1, 2020 to September 30, 2021, during the midst of the third wave, and included pregnant women in the pre-vaccination and early vaccination era, in order to capture the peak incidence of pregnant women with COVID-19 and probable incidence of vertical transmission.

Materials and methods

Study design and participants

This was a retrospective observational study covering the period from October 1, 2020 to September 30, 2021.

The center involved in the current study, Sungai Buloh Hospital, is a multispecialty government-funded hospital located in Selangor. Sungai Buloh Hospital was chosen as the study center in view of it being the designated COVID-19 center, covering areas with a high population density with high live birth rates and peak COVID-19 cases during the study period.

Cases from Selangor State and the Federal Territory of Kuala Lumpur accounted for the majority of COVID-19 cases in the country during the third wave (COVID NOW, 2022). During the study period, Sungai Buloh Hospital was a dedicated COVID-19 center for Selangor and the two federal territories of Kuala Lumpur and Putrajaya. Both of these federal territories are enclaves in the state of Selangor; collectively these three areas are known as Klang Valley.

As of the second quarter of 2021, the total Malaysian population was 32.7 million. The population of Selangor, the most populous state in Malaysia, stood at about 6.56 million, and the populations of the federal territories of Kuala Lumpur and Putrajaya were 1.75 million and 0.12 million, respectively. In addition, the total live births per year in Malaysia was 470 195 (crude birth rate of 14.4 per 1000 population), with Selangor contributing 93 257 per year (state with the highest number of live births) and the federal territories of Kuala Lumpur and Putrajaya contributing 23 087 and 2142 live births per year, respectively (Department of Statistics Malaysia, 2021Department of Statistics Malaysia, 2022). The maternity unit at Sungai Buloh Hospital saw 11 413 live births per year as of 2018 (pre-pandemic), which reduced to 4115 live births in 2020.

According to the local government authority, all pregnant women in Klang Valley with COVID-19 who were near term or had any obstetric indications such as in labor, were to be admitted to the obstetric unit of Sungai Buloh Hospital. However, as COVID-19 cases surged among pregnant women, beyond the capacity of this hospital, pregnant women with COVID-19 of category 1 and 2 were diverted to their nearest hospital for admission. These hospitals included other government hospitals, university hospitals, and private health centers in Klang Valley.

All babies born to mothers with COVID-19 in Sungai Buloh Hospital and all of the other hospitals in Klang Valley were referred and admitted to the neonatal unit, Sungai Buloh Hospital for further isolation and management (Ministry of Health Malaysia Press statement, 2021). The capacity of the neonatal unit is up to a maximum of 90 beds per day.

All neonates who were born to pregnant mothers with COVID-19 and admitted to the neonatal unit, Sungai Buloh Hospital during the study period were recruited for this study. The data were extracted from the electronic hospital information system (E-HIS). Data on maternal demographics, labor and delivery information, and neonatal information were obtained.

Case definition

A case was defined as the newborn of a pregnant woman who had confirmed COVID-19 at the time of delivery. Confirmation of COVID-19 in these women was either by positive molecular test (SARS-CoV-2 real-time reverse-transcriptase PCR (RT-PCR) or rapid molecular test) or a positive rapid antigen test kit (RTK-Ag) in predetermined areas/localities with a prevalence of COVID-19 >10% (Ministry of Health Malaysia, 2020).

The duration of maternal illness was defined by the onset of symptoms or date tested positive, whichever was earlier from the time of childbirth. Illness severity was categorized as follows: category 1: asymptomatic; category 2: symptomatic without pneumonia; category 3: symptomatic with pneumonia, without requirement for supplemental oxygen; category 4: symptomatic with pneumonia, requiring supplemental oxygen; category 5: critically ill with multi-organ involvement (Ministry of Health Malaysia, 2020). The severity of maternal illness was assigned based on the symptoms experienced at the time of childbirth. Maternal antenatal problems such as diabetes mellitus and hypertension were also documented.

Labor and delivery information retrieved included the mode of delivery, any labor onset, rupture of the membranes, antepartum hemorrhage, birthweight and gestational age, and Apgar scores obtained at 1 minute and 5 minutes. Apgar scores were classified into two groups: 0–5 and 6–10. Exposure to the mother after delivery included any skin to skin contact, breastfeeding, or rooming in with the mother.

Neonates were diagnosed as SARS-CoV-2-positive if they had a positive SARS-CoV-2 RT-PCR test of a nasopharyngeal swab sample (Ministry of Health Malaysia, 2020). They were then further classified into neonatal infection acquired intrapartum or neonatal infection acquired postpartum, according to the classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates proposed by Shah et al., with some modification (Shah et al., 2020).

For neonatal infection acquired intrapartum, a confirmed case was defined as a positive nasopharyngeal swab SARS-CoV-2 PCR at birth (collected after cleaning the baby) followed by a positive nasopharyngeal swab at 24–48 hours of age. A possible case was defined as a positive nasopharyngeal swab SARS-CoV-2 PCR at birth (collected after cleaning the baby) and not at 24–48 hours. A non-infected case was defined as one where there was no detection of the virus by PCR in a nasopharyngeal swab at birth and also at 24–48 hours.

For neonatal infection acquired postpartum, a confirmed case was defined as a positive nasopharyngeal swab SARS-CoV-2 PCR at >48 hours after birth in a neonate with a negative nasopharyngeal swab SARS-CoV-2 PCR at birth. A possible case was defined as a positive nasopharyngeal swab SARS-CoV-2 PCR at >48 hours after birth in a neonate who was not tested at birth. A non-infected case was defined as no detection of the virus by PCR in a nasopharyngeal/rectal swab at >48 hours after birth and other cause identified. The reason for the modification to the classification system originally proposed by Shah et al. is elaborated in the Discussion section.

SARS-CoV-2-positive neonates were further evaluated for clinical severity, blood investigation, radiological findings, and treatment received.

Neonates who were exposed to another source of COVID-19 other than their mother were excluded. Neonates of mothers who tested SARS-CoV-2-positive after delivery were also excluded.

Local protocols

Universal screening testing for SARS-CoV-2 was done for all pregnant women requiring admission to hospitals in Malaysia, as pregnant women with undiagnosed asymptomatic COVID-19 pose a high risk of transmission to their newborns, healthcare workers, and other patients (Hashim et al., 2022).

During the study period, cesarean section was the primary mode of delivery for all mothers diagnosed with COVID-19, unless the mother came in with impending labor. All cesarean sections were conducted in a designated operation theater for COVID-19 patients. The obstetrician, along with the other operation theater staff involved, wore full personal protective equipment during the delivery.

For mothers with impending labor, a spontaneous vaginal delivery was allowed provided there were no obstetric contraindications. Obstetricians and the midwives involved wore full personal protective equipment during the delivery. The mothers were asked to wear a mask during the delivery process.

The neonatal team was referred for standby for delivery. The neonatal team donned protective personal equipment before standby. Resuscitation of the neonate was conducted in an adjacent room. If this was not feasible, the Resuscitaire was physically separated from the mother's delivery area by a distance of at least 2 meters.

After the baby was delivered, the baby was immediately handed to the standby neonatal team for initial stabilization and resuscitation, as per neonatal resuscitation program (NRP) guidelines. The baby was wiped dry and cleaned. The first nasopharyngeal SARS-CoV-2 PCR was taken at birth after cleaning. Post stabilization, the neonate was transferred into the transport incubator without undergoing any non-urgent neonatal care.

The neonate was then transported via a predefined route and elevator for minimal exposure. All neonates were admitted to the neonatal unit of a designated COVID-19 hospital, such as Sungai Buloh Hospital, for isolation and further monitoring.

If the neonate was delivered in a non-dedicated COVID-19 center, the neonate was transferred to the neonatal unit of a designated COVID-19 hospital from the delivery room. The average transfer time to the neonatal unit at Buloh Hospital was within 3–6 hours. However, there were exceptional cases where neonates who were unstable for transport were first stabilized in the undesignated center before transfer to the unit. There were also cases of late transfer due to late confirmation of maternal pre-delivery nasopharyngeal SARS-CoV-2 test results.

All neonates at risk were temporarily separated from their mothers to avoid postpartum transmission of infection from maternal respiratory secretions. However, some undesignated centers that also catered for non-COVID deliveries had limited spaces for isolation, thus the neonates were allowed to room-in with the mother while waiting for transport to the neonatal unit. Adequate measures were taken, including advice for the mother to wear a mask and to exercise hand hygiene when handling their baby.

In the neonatal unit of Sungai Buloh Hospital, symptomatic neonates were isolated in an isolation room. Asymptomatic neonates were cared for in incubators or an open cot in a well-ventilated space, separated at least 1 to 2 meters apart. Attending medical personnel wore full personal protective equipment. As the medical personnel provided the necessary care, i.e. feeding, changing diapers, etc., they changed their outer apron and gloves and performed strict hand hygiene before handling the next neonate.

High-risk neonates with a history of exposure to their mother post-delivery were placed in incubators for isolation and were cared for in a different section to the rest of the neonates.

During the study period, no visitor was allowed to come into the neonatal unit. Full updates on the neonate's progress were given to the parents via phone.

Expressed breast milk from mothers with COVID-19 was allowed in special circumstances, for premature infants or term infants who were unable to tolerate formula milk feeding. Mothers who needed to express breast milk for their newborn infants were advised regarding proper hand washing (to wash their hands before touching the breast, breast pump, or bottles) and to wear a mask while expressing breast milk (Centers for Disease Control and Prevention, 2021).

All neonates had their first nasopharyngeal swab for SARS-CoV-2 RT-PCR obtained at birth after cleaning. However, for some neonates who were transferred in from an undesignated center, it was not possible to obtain their first nasopharyngeal swab at birth in view of limitations of the center. For this group of neonates, the first swab was taken immediately upon admission to the neonatal unit at Sungai Buloh Hospital. This resulted in some variation in the timing of the first swab, which is described later in the Results section.

Repeat testing was done at 36–48 hours after the first test. If both tests were reported as negative, the neonate was off-tagged and discharged to the caregivers who were well and not under quarantine.

Newborns who remained in the neonatal ICU due to other reasons (e.g. prematurity) despite two negative SARS-CoV-2 PCR were re-screened by nasopharyngeal SARS-CoV-2 PCR if they become symptomatic.

If a neonate tested positive, those who were asymptomatic were nursed in a closed incubator; this cohort of neonates were kept in a separate space with other positive neonates. They were monitored closely for any progression of symptoms, and supportive treatment was given accordingly.

However, due to increasing numbers of neonates who had been exposed to their mother post-delivery being transferred from some undesignated centers, the neonatal unit protocols at Sungai Buloh Hospital were adjusted in May 2021 to keep those neonates in a closed incubator for at least 10 days from exposure and to perform the second testing on day 8 of life or earlier if symptomatic, instead of at 36–48 hours after first testing.

During admission, all neonates were monitored clinically for any signs or symptoms of infection. Blood investigations and radiological chest X-rays were not routinely performed for asymptomatic newborns. For newborns who were symptomatic at birth or later during admission, relevant investigations were done including blood taking and imaging.

Statistical analysis

Maternal and neonatal characteristics were summarized using descriptive statistics, such as the frequency and percentage (%) for categorical variables and the mean and standard deviation (SD) for continuous variables. The association of maternal and neonatal characteristics with SARS-CoV-2 positivity was investigated using the odds ratio (OR), which indicated the risk of SARS-CoV-2 positivity. The value of the OR was computed using a univariable logistic regression model, and the 95% confidence interval (95% CI) and *P*-value were also reported. An OR was considered statistically significant if the associated *P*-value was less than 0.05. The statistical analysis was performed using R version 4.1.0 with the gmodels package (R Core Team, 2021; Gregory et al., 2018). The rationale for using univariable logistic regression was the small number of SARS-CoV-2-positive neonates (23 out of 766), which did not provide sufficient power to proceed with a multiple regression analysis to control for confounding effects.

Ethical considerations

The study was registered in the National Medical Research Register (NMRR-20-580-54339) and was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

Results

Neonatal characteristics (Table 1)

A total of 766 babies were included in this study, with an almost equal sex distribution. Most of the neonates were delivered by cesarean section (n = 602, 78.6%). More than two-thirds (n = 548, 71.5%) were delivered in Sungai Buloh Hospital, which is a dedicated COVID-19 center, while the remaining babies (n = 218, 28.5%) were born in other non-COVID dedicated centers before being transferred to Sungai Buloh

Hospital. There were no reported cases of skin-to-skin contact for babies born in Sungai Buloh Hospital, while there were 40 (5.2%) cases for babies born in other hospitals.

The majority of the babies were born at term (n = 570, 74.4%) and had a birth weight of ≥2500 g (n = 564, 73.6%). However, preterm birth was significant (n = 196, 25.6%), with only a minority being born prior to 28 weeks (n = 10, 1.3%) and having a birth weight of <1000 g (n = 13, 1.7%). The mothers of half of the babies (49.3%) presented in labor, and about 9.7% of the mothers presented with rupture of the membranes, with 26 (3.4%) having prolonged rupture of the membranes of ≥18 hours. Only 1.6% mothers reported antepartum hemorrhage.

The majority of babies had a recorded Apgar score of more than 5 at both 1 and 5 minutes of life, with a mean score 8.1 at 1 minute and 9.3 at 5 minutes of life. The overall neonatal mortality rate in this series was 1.0% (eight deaths). The median length of hospitalization for the neonates was 8 days (interquartile range 4 days).

Maternal characteristics (Table 2)

The 766 neonates were born to 753 pregnant women with COVID-19; there were 13 pairs of twin pregnancies. Overall, 659 (88%) mothers were Malaysian citizens, while 92 (12.3%) were non-Malaysian citizens. In this series, most of the pregnant women (n = 690, 91.6%) were in the age group 21–40 years old. They presented mainly with asymptomatic to mild COVID-19 illness at the time of delivery: 389 (51.6%) were category 1 and 219 (29.1%) were category 2. Eighty-nine (11.8%) mothers presented with category 5 illness. The majority of the pregnant women (n = 579, 76.9%) presented with a short duration of COVID-19-related symptoms, up to 7 days prior to the onset of labor.

Serial nasopharyngeal SARS-CoV-2 PCR results (Table 3)

All babies, 766 (100%), had the first SARS-CoV-2 RT-PCR swab, while 763 (99.6%) had the second SARS-CoV-2 RT-PCR swab performed. A total of 743 (97%) neonates tested negative in both the first and second test.

Overall, 23 (3%) of the neonates included in this study tested positive with at least one positive nasopharyngeal swab SARS-CoV-2 PCR taken within the first 8 days of life. According to the modified classification applied and the case definition for SARS-CoV-2 infection in neonates adapted from Shah et al., there were three (0.4%) confirmed and four (0.5%) probable neonatal infections acquired intrapartum, and seven (0.9%) confirmed neonatal infections acquired postpartum.

The remaining nine SARS-CoV-2-positive neonates did not fit within the classification system. Five neonates had a suspected neonatal infection acquired intrapartum but did not fulfill the modified classification: two neonates tested positive at birth but were not tested again , another two neonates tested positive at birth and were tested positive again >48 hours of life, and one neonate was first tested positive at 24 hours of life and tested positive again >48 hours of life. The other four neonates who did not fit within the classification system had a suspected neonatal infection acquired postpartum. No swab was taken at birth; the first swab taken at >48 hours of life was negative, but subsequent repeated swabs were positive, with the latest SARS-CoV-2-positive test on day 8 of life.

Associations of maternal and neonatal characteristics with infection outcome

The association of SARS-CoV-2 positivity in neonates with various risk factors was analyzed (Table 4) and it was found that maternal antepartum hemorrhage played a significant role in this series, with an OR of 7.33 (95% CI 1.08–30.20, P = 0.014). The place of delivery appeared to be an important determining factor for SARS-CoV-2 positivity in neonates, with an OR of 7.64 (95% CI 3.13–21.4, P < 0.001). In

Table 1
Neonatal characteristics—neonates born to mothers with COVID-19.

Characteristics	Category	n	(%)
Sex	Female	363	(47.4)
	Male	403	(52.6)
Mode of delivery	Cesarean section	602	(78.6)
	Vaginal delivery	164	(21.4)
Ethnicity	Malay	577	(75.3)
	Indian	53	(6.9)
	Chinese	31	(4.0)
	Others	105	(13.7)
Place of delivery	Sungai Buloh Hospital	548	(71.5)
	Other hospital	218	(28.5)
Gestation, weeks	<28	10	(1.3)
	28–31	42	(5.5)
	32–33	33	(4.3)
	34–36	111	(14.5)
	≥37 (term)	570	(74.4)
Birth weight, g	<1000	13	(1.7)
	1000–1499	30	(3.9)
	1500–2499	159	(20.8)
	≥2500	564	(73.6)
Apgar score 1 minute	0–5	93	(12.1)
	6–10	673	(87.9)
Apgar score 5 minutes	0–5	45	(5.9)
	6–10	721	(94.1)
Maternal labor onset	Yes	377	(49.3)
Maternal antepartum hemorrhage	Yes	12	(1.6)
Maternal pre-labor rupture of the membranes	<18 hours	48	(6.3)
	≥18 hours	26	(3.4)
	No	688	(89.8)
Exposure to mother	No	726	(94.8)
	Yes	40	(5.2)
Survival to discharge	Yes	758	(99.0)
	No	8	(1.0)
Length of hospital stay, days	Median (IQR)	8	(4)
	0–5	188	(24.5)
	6–10	420	(54.8)
	11–20	97	(12.7)
	21–30	18	(2.3)
	>30	42	(5.5)
	Unknown	1	(0.1)

IQR, interquartile range.

Table 2
Maternal characteristics—neonates born to mothers with COVID-19.

Characteristics	Category	n	(%)
Age, years	15–20	30	(4.0)
	21–30	354	(47.0)
	31–40	336	(44.6)
	41–50	23	(3.1)
	Unknown	10	(1.3)
Ethnicity	Malay	566	(75.2)
	Chinese	31	(4.1)
	Indian	53	(7.0)
	Others	13	(1.7)
	Non-Malaysian	90	(12.0)
Type of pregnancy	Singleton	740	(98.3)
	Twin	13	(1.7)
Comorbidities	Diabetes mellitus	256	(34.0)
	Hypertension	39	(5.2)
Onset of maternal illness prior to delivery, days	0–7	579	(76.9)
	8–14	156	(20.7)
	≥15	6	(0.8)
	Unknown	12	(1.6)
Maternal COVID-19 category of illness	1	389	(51.6)
	2	219	(29.1)
	3	24	(3.2)
	4	30	(4.0)
	5	89	(11.8)
	Unknown	2	(0.3)

Table 3
Serial nasopharyngeal SARS-CoV-2 PCR results.

Initial PCR at birth (<12 h)	Repeated PCR 36–48 h	>48 h	Number of patients	Conclusion
Positive	Positive	Not taken	3	Confirmed neonatal infection acquired intrapartum
Positive	Negative	Not taken	4	Possible neonatal infection acquired intrapartum
Positive	Not taken	Not taken	2	Inconclusive neonatal infection
Positive	Not taken	Negative	2	acquired intrapartum
Not taken[a]	Positive[b]	Positive	1	
Negative	Not taken	Positive	7	Confirmed neonatal infection acquired postpartum
Not taken[a]	Not taken	Positive	4	Inconclusive neonatal infection acquired postpartum
Negative	Negative		743	Not infected

First nasopharyngeal swab for SARS-CoV-2 RT-PCR obtained at birth whenever possible. A repeat test was done 36–48 hours after the first test, except in those with exposure to their mother postpartum, for whom a repeat test was done on day 8 of life.

[a] Not possible to take the first swab at birth, due to the limitation of some non-dedicated COVID centers to obtain a swab at birth and a delay in transfer of the neonate to the study center.

[b] First nasopharyngeal SARS-CoV-2 PCR was taken at 24 hours of life.

Table 4
Associations of maternal and neonatal characteristics with the neonatal infection outcome.

Characteristic	Category	Neonatal SARS-CoV-2 infection				OR (95% CI)	*P*-value
		Negative		Positive			
		n	(%)	*n*	(%)		
Maternal							
Diabetes mellitus	No	486	(65.4)	18	(78.3)	Reference	
	Yes	257	(34.6)	5	(21.7)	0.53 (0.17, 1.35)	0.215
Hypertension	No	704	(94.8)	22	(95.7)	Reference	
	Yes	39	(5.2)	1	(4.3)	0.82 (0.04, 4.10)	0.855
Rupture of membrane	No	669	(90.4)	19	(86.4)	Reference	
	Yes	71	(9.6)	3	(13.6)	1.48 (0.34, 4.49)	0.535
Maternal COVID-19	Category 1 and 2	601	(81.1)	18	(78.3)	Reference	
severity on admission	Category 3, 4 and 5	140	(18.9)	5	(21.7)	1.19 (0.39, 3.05)	0.732
Days of illness	0–7	569	(77.7)	20	(90.9)	Reference	
	>8	163	(22.3)	2	(9.1)	2.86 (0.82, 18.1)	0.159
Neonatal							
Sex	Female	355	(47.8)	8	(34.8)	Reference	
	Male	388	(52.2)	15	(65.2)	1.71 (0.74, 4.31)	0.224
Place of delivery	Sungai Buloh Hospital	542	(72.9)	6	(26.1)	Reference	
	Other hospital	201	(27.1)	17	(73.9)	7.64 (3.13, 21.4)	<0.001
Gestational age	Term (≥37 weeks)	556	(74.8)	14	(60.9)	Reference	
	Pre-term (<37 weeks)	187	(25.2)	9	(39.1)	0.52 (0.23, 1.27)	0.137
Birth weight, g	≥2500	550	(74.0)	14	(60.9)	Reference	
	<2500	193	(26.0)	9	(39.1)	0.55 (0.24, 1.33)	0.164
Mode of delivery	Cesarean section	586	(78.9)	16	(69.6)	Reference	
	Vaginal delivery	157	(21.1)	7	(30.4)	1.63 (0.62, 3.90)	0.288
Exposure to mother	No	707	(95.2)	19	(82.6)	Reference	
	Yes	36	(4.8)	4	(17.4)	4.13 (1.15, 11.70)	0.014
Antepartum hemorrhage	No	733	(98.7)	20	(90.9)	Reference	
	Yes	10	(1.3)	2	(9.1)	7.33 (1.08, 30.20)	0.014
Apgar score 1 minute	0–5	87	(11.7)	6	(26.1)	Reference	
	6–10	656	(88.3)	17	(73.9)	0.38 (0.15, 1.06)	0.045
Apgar score 5 minutes	0–5	40	(5.4)	5	(21.7)	Reference	
	6–10	703	(94.6)	18	(78.3)	0.20 (0.08, 0.65)	0.003

OR, odds ratio; CI, confidence interval.

this series, 7.8% (17/218) of the neonates born in non-COVID-19 centers were positive for SARS-CoV-2 compared to 0.01% (6/548) of those born in Sungai Buloh Hospital. Exposure to the mother at birth was also significantly associated with SARS-CoV-2 positivity in neonates, with an OR of 4.13 (95% CI 1.15–11.70, $P = 0.014$). Interestingly, a higher severity of maternal COVID-19 category illness was not significantly associated with neonatal SARS-CoV-2 positivity. Also, neither the days of maternal illness prior to delivery nor the mode of delivery was found to have any significant association with neonatal SARS-CoV-2 positivity. It was observed that the SARS-CoV-2 positivity rate among neonates with a higher 5-minute Apgar score (6–10) was significantly lower (0.025%, n =18/721) as compared to that of the neonates with a lower 5-minute Apgar score (0–5), which stood at 11.1% (n = 5/45). This association was significant, with an OR of 0.20 (95% CI 0.08–0.65, $P = 0.003$).

Mothers with severe COVID-19 of category 4 and 5 were at significantly higher risk of having a preterm delivery (n = 95/243), with an OR of 6.2 (95% CI 4.1–9.6, $P < 0.0001$) (Table 5).

Characteristics of SARS-CoV-2-positive neonates and their mothers (n = 23) (Tables 6 and 7)

Eleven (47.8%) mothers of SARS-CoV-2-positive neonates presented with labor onset before delivery. These mothers presented on average at day 4 of illness at the point of delivery, with an almost equal number

Table 5
Association between maternal COVID-19 severity and preterm delivery.

COVID-19 severity	Gestational week ≥37 weeks	<37 weeks	OR (95% CI)	*P*-value
Category 1	359 (57.8)	37 (25.9)	Reference	
Category 2–3	114 (18.4)	11 (7.7)	0.9 (0.4, 1.8)	0.855
Category 4–5	148 (23.8)	95 (66.4)	6.2 (4.1, 9.6)	<0.0001

OR, odds ratio; CI, confidence interval.

Table 6
Maternal characteristics—mothers of SARS-CoV-2-positive neonates (n = 23).

Maternal age in years, median (IQR)		30.0 (8.0)
Ethnicity, *n* (%)	Malay	19 (82.6)
	Indian	1 (4.3)
	Non-Malaysian	3 (13)
Maternal comorbidities, *n* (%)	None	14 (60.9)
	Premature rupture of the membranes	3 (13)
	Diabetes mellitus	5 (21.7)
	Hypertension	2 (8.7)
	Antepartum hemorrhage	2 (8.7)
Day of illness, median (IQR)		4.0 (5.0)
Maternal severity of COVID-19, *n* (%)	Category 1	11 (47.8)
	Category 2	7 (30.4)
	Category 3	0 (0)
	Category 4	2 (8.7)
	Category 5	3 (13)
Contraction pain, *n* (%)	Yes	11 (47.8)
	No	12 (52.2)
Mode of delivery, *n* (%)	Vaginal delivery	7 (30.4)
	Cesarean section	16 (69.6)

IQR, interquartile range.

Table 7
Neonatal characteristics—neonates with confirmed SARS-CoV-2 infection (n = 23).

Gestation at delivery, *n* (%)	Term	14 (60.9)
	Preterm	9 (39.1)
	34–36 weeks 5 days	4 (17.4)
	32–33 weeks 5 days	0 (0)
	28–31 weeks 5 days	5 (21.7)
	<28 weeks	0 (0)
Apgar score, median (IQR)	At 1 minute	9.0 (1.0)
	At 5 minutes	10.0 (1.0)
Birth weight, g, median (IQR)		2890 (750)
Sex, *n* (%)	Male	15 (65.2)
	Female	8 (34.8)
Exposure to mother, *n* (%)	Yes	4 (17.4)
	No	19 (82.6)
Feeding, *n* (%)	Expressed breast milk	3 (13.0)
	Formula milk	20 (87)
Neonatal severity of illness, *n* (%)	Category 1	12 (52.2)
	Category 2	1 (4.3)
	Category 3	0 (0)
	Category 4	3 (13.0)
	Category 5	7 (30.4)
Highest mode of ventilation support, *n* (%)	Invasive	6 (26.1)
	Non-invasive	3 (13.0)
	Nasal prong oxygen	1 (4.3)
	Room air	13 (56.5)
Laboratory investigations, mean (SD)	Hb (g/dl)	17.4 (2.5)
	TWBC ($\times 10^9$/l)	11.9 (4.2)
	ALC ($\times 10^9$/l)	4.3 (2.3)
	ANC ($\times 10^9$/l)	4.4 (2.1)
	Platelets ($\times 10^9$/l)	295.4 (78.4)
	AST (U/l)	34.1 (21.2)
	ALT (U/l)	10.8 (2.7)
Chest radiography, *n* (%)	Abnormal	10 (43.5)
	Normal	13 (56.5)
Treatment given, *n* (%)	Yes	14 (60.9)
	No	9 (39.1)
Treatment breakdown, *n* (%)	Antibiotic	14 (60.9)
	Antenatal steroid	4 (17.4)
	Postnatal steroid	1 (4.3)
	Surfactant	5 (21.7)
	Inhaled nitric oxide	1 (4.3)
	Aspirin	1 (4.3)
	Antiviral	0 (0)
	Immunoglobulin	3 (13.0)
Survival to discharge, *n* (%)		22 (95.7)

ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; Hb, hemoglobin; IQR, interquartile range; SD, standard deviation; TWBC, total white blood cell count.

of asymptomatic (n = 11, 47.8%) and symptomatic mothers (n = 13, 52.2%).

Nine (39.1%) babies were born preterm, while 14 (60.9%) were born at term. Among the affected neonates, 15 (65.3%) were male and eight (34.8%) were female. The affected neonates had an average Apgar score of 7 at 1 minute and 8 at 5 minutes. There were four (17.4%) neonates who had exposure to their mother post-delivery. Only three babies (13.0%) received expressed breast milk from their own mothers.

The majority (n = 12, 52.2%) of the SARS-CoV-2-positive neonates were asymptomatic (category 1). The remaining neonates were category 2 (n = 1, 4.3%), category 4 (n = 3, 13.0%), or category 5 (n = 7, 30.4%). Ten neonates (43.5%) required some form of ventilatory support, of whom six required invasive ventilation; three neonates required non-invasive ventilation and one had nasal prong oxygen. Blood investigations were relatively unremarkable except for findings of lymphopenia. Chest X-rays were done for 10 (43.5%) newborns, which all showed abnormalities.

Fourteen (60.9%) neonates received treatment, mainly antibiotics. Other treatments were antenatal steroids (four neonates), surfactant (five neonates), and immunoglobulin (three neonates). One neonate received postnatal steroids, inhaled nitric oxide, and aspirin. None of the neonates were given antiviral treatment. The survival rate among the SARS-CoV-2-positive neonates was 95.7%.

Discussion

Overall key characteristics and outcomes

Mode of delivery

The high rate of cesarean section recorded in this study, at 78.6% (602/766), is in line with the local protocol during the study period, whereby any pregnant woman with COVID-19 in labor or at term was scheduled for a cesarean section unless a vaginal delivery was imminent. However, this is in strong contrast to the pre-pandemic era in Sungai Buloh Hospital: with total live births of 11 613 per year in 2018, the rate of cesarean section was 30.6% (n = 3558) while the rate of vaginal delivery was 69.4% (n = 8055). Around 15.1% (116/766) of pregnant women who had severe COVID-19 disease required an imminent delivery to improve the oxygenation, which partly increased the need for cesarean section. However, many asymptomatic mothers and laboring mothers who would normally have delivered vaginally were also subjected to cesarean section due to the main worry of the risk of vertical transmission, which could contribute to neonatal morbidity and mortality (Dashraath et al., 2020). Of note, there was no significant association of an increased risk of infection according to the mode of delivery in this study. This finding supports those of a systematic review study, in which

it was concluded that the mode of delivery should be individualized and based on disease severity and obstetric indications (Cai et al., 2021). There is also concern surrounding the risk of transmission through respiratory droplets during the process of vaginal delivery posing a higher risk of COVID-19 to attending medical health personnel as compared to a cesarean delivery (Hashim et al., 2022).

Preterm delivery

In the study population, an increase in preterm delivery rate was observed among neonates born to pregnant mothers with COVID-19, accounting for 25% (n = 196/766). This is in comparison to a preterm birth rate of 16.8% at Sungai Buloh Hospital in the pre-pandemic era (in a total of 11 613 live births in 2018).

This finding is in agreement with that of a large population-based study performed in United States, in which it was found that the risk of very preterm birth, occurring at <32 weeks of gestation, was 60% higher for people infected with SARS-CoV-2 at some point in their pregnancy, while the risk of giving birth at <37 weeks (all preterm births) was 40% higher in those who were infected. For those who had hypertension, diabetes, and/or obesity as well as COVID-19, the risk of preterm birth increased 160% (Karasek et al., 2021). In another study, it was observed that pregnant women with symptomatic COVID-19 were more than twice as likely to have a preterm delivery when compared to those without SARS-CoV-2 infection (Blitz et al., 2021).

In addition, the current study also found that preterm delivery was more frequent among the SARS-CoV-2-positive neonates at 39.1% (n = 9/23) when compared to the SARS-CoV-2-negative neonates at 25.2% (n = 187/743).

Preterm birth is associated with many challenging outcomes for pregnant women and neonates; moreover, very preterm births carry the highest risk of complications. The overall neonatal mortality rate in the current series was 1.0% (eight deaths). All of the neonatal deaths were in premature babies with a gestational age within the range of 23 to 30 weeks. Only one of the eight neonates who died tested SARS-CoV-2-positive. The causes of mortality were mainly due to complications from prematurity, such as intraventricular hemorrhage, pulmonary hemorrhage, and necrotizing enterocolitis. This further highlights the importance of preventive measures against COVID-19 among pregnant women, including vaccination, in order to indirectly prevent preterm birth, and the need to guide patient counseling regarding the COVID-19-related pregnancy risk.

Vertical transmission

Peripartum 'vertical transmission' of SARS-CoV-2 infection can result from intrauterine transmission (hematogenous spread from the placenta or viral particles in the amniotic fluid), intrapartum transmission (exposure to infected maternal blood, infected maternal feces, or infected maternal genital tract secretions), or immediate postnatal transmission (from maternal respiratory secretions or possibly breastmilk) (Blumberg et al., 2020).

There are differing recommendations on the timing of nasopharyngeal swab SARS-CoV-2 PCR to make a diagnosis of SARS-CoV-2 infection in neonates.

The SARS-CoV-2 PCR assay detects the presence of virus genetic fragments and does not assess whether there is a replicating virus. Thus, a single positive RT-PCR in a respiratory sample from a neonate may indicate either a true-positive result, i.e. active viral replication in an infected patient, or a false-positive result, i.e. transient superficial contamination of the neonate's nares, nasopharynx, and/or oropharynx from viral fragments acquired during passage through the birth canal or from the immediate postnatal environment that does not actually cause infection (Blumberg et al., 2020). There are also concerns that early testing at birth may lead to false-positive results as mentioned above, or false-negative results, e.g. RNA may not yet be detectable immediately after exposure following birth (Centers for Disease Control and Prevention, 2021).

The classification system and case definition for SARS-CoV-2 in pregnant women, fetuses, and neonates of Shah et al. was adopted in the present study (Shah et al., 2020). According to this classification, testing at birth is important to differentiate between intrapartum and postpartum acquired infection. In the present authors' opinion, testing at-risk newborns at birth enables optimal neonatal management and cohorting of infected patients to prevent the transmission of infection.

However, the presence of clinical features, included in the original classification system by Shah et al., was removed as a criterion in the current study. This is because there was a significant number of patients who tested positive at birth who were symptomatic due to clinical features other than those of COVID-19. In addition, there was also another group of patients who were asymptomatic with negative nasopharyngeal swab SARS-CoV-2 PCR at birth, but had positive nasopharyngeal swab SARS-CoV-2 PCR at more than 48 hours.

In this study, there were six neonates who tested SARS-CoV-2-positive in the first swab, but subsequent swabs were negative. This suggests the possibility of a false-positive result for the first test or a false-negative second test.

It was not possible to diagnose intrauterine infection in this study, as no amniotic fluid, placental tissue, umbilical cord or neonatal blood was sent for detection of SARS-CoV-2 PCR.

In the study population, an increasing number of neonates were exposed to their mother post-delivery (40/766) due to limitations of isolation rooms in the undesignated COVID-19 centers. Also, local protocols were slightly adjusted in May 2021 to keep those neonates who were at higher risk in a closed incubator for at least 10 days from exposure and to perform second testing on day 8 of life or earlier if symptomatic, instead of at 48 hours after first testing.

The rationale behind these changes was to ensure that no neonates who turned SARS-CoV-2-positive later after the incubation period were missed. Ideally testing should be done at birth, second testing by 48 hours of life, and third testing on day 8 of life and whenever the child turns symptomatic during the period of isolation. However, multiple testing would have placed a significant burden on health care workers and health care costs during the time of the pandemic.

There is concern that if a neonate turns SARS-CoV-2-positive on day 8 of life, this would have resulted from postnatal human-to-human transmission other than from their mother. But, as these higher risk neonates were kept in closed incubator nursing and isolated from other visitors with a strict infection control protocol at Sungai Buloh Hospital, it is believed that if they did turn SARS-CoV-2-positive, it would have been acquired postpartum from the mother rather than from another source.

Risk factors associated with vertical transmission

A higher risk of SARS-CoV-2 positivity was observed in babies born in non-designated COVID centers. Among the 40 out of 766 (5.2%) neonates with exposure to their mother immediately after birth, four (10%) tested SARS-CoV-2-positive. This is in contrast to the neonates without exposure to their mother post-delivery, of whom 11 out of 726 (1.5%) tested SARS-CoV-2-positive. This could be due to a lack of strict infection control protocols leading to increased transmission from the mother. Studies have shown that if a strict infection control protocol is practiced, even if rooming in or the mother is breastfeeding, the transmission risk can be minimized (Salvatore et al., 2020). However, this would sometimes be difficult to control in the midst of a large surge of infected pregnant women.

Maternal antepartum hemorrhage may lead to contamination of the fluid with viral particles from the mother's blood. The ingestion and/or inhalation of this infected fluid during the peripartum period could lead to viral particle transmission.

The current study found that infants with a 5-minute Apgar score below 6 had a higher risk of SARS-CoV-2 infection. However there is another study that has suggested that Apgar scores below 7 are likely

to be associated with severe maternal COVID-19 during delivery rather than neonatal COVID-19 (Melissa et al., 2022).

Characteristics of newborns with a vertically transmitted SARS-CoV-2 infection

The majority of infected neonates were asymptomatic or had mild symptoms. Ten SARS-CoV-2-positive neonates required ventilatory support. However, only one of these 10 neonates had respiratory issues attributed solely to COVID-19. The other babies required ventilatory support as a consequence of their prematurity or maternal sedation. Our experience in using combination treatment of postnatal steroids with methylprednisolone, aspirin, immunoglobulin, and inhaled nitric oxide was limited to a baby boy who was confirmed to have a SARS-CoV-2 infection acquired intrapartum and had a category 5 illness. He was born at term, with a birth weight of 3.12 kg, and was not exposed to his mother postnatally; however, he had ingested maternal blood intrapartum. This neonate required a high ventilator setting (high frequency oscillation ventilator), which he was gradually weaned off, and he was discharged well without any oxygen support on day 110 of life. None of the patients received antiviral treatment. More studies are needed to evaluate the efficacy of these combination treatments among neonatal groups. The outcomes of the infected neonates were relatively good; the survival rate among neonates with SARS-CoV-2 infections was 95.7%. The cause of death for the one SARS-CoV-2-positive neonate who died was not directly COVID-19-related, but was due to complications of prematurity, which is an indirect consequence of maternal COVID-19.

Conclusions

There is a risk of SARS-CoV-2 positivity and an increased risk of prematurity in neonates of pregnant women with COVID-19, which contribute to neonatal morbidity and mortality. Although, the outcomes of the neonates with SARS-CoV-2 were generally good, with asymptomatic infections or relatively mild symptoms, there were still significant numbers who were affected directly or indirectly due to maternal COVID-19. Therefore, preventive measures, especially vaccination, are of paramount importance to protect against the known risk of COVID-19 to pregnant women and their newborns.

Limitations

There are limitations to this study that should be acknowledged. There was some inconsistency in the timing of the first swab and subsequent swabs taken, leading to some diagnostic uncertainty. As this was a retrospective study, it was difficult to standardize the practice, especially in the rapidly evolving COVID-19 pandemic, and missing data would also be unavoidable. Furthermore, it was not possible to establish intrauterine transmission of infection in this study, as maternal placenta tissue, amniotic fluid, vaginal secretions, and umbilical cord blood were not tested for SARS-CoV-2. Also, the neonates were not tested for IgM or IgG antibodies to SARS-CoV-2.

A larger prospective study including neonates born to mothers without COVID-19 as a comparison group would be beneficial to come to better conclusions and improve understanding.

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Conflict of interest

We declare no conflict of interest.

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Ethical approval

The study was registered in the National Medical Research Register (NMRR-20-580-54339) and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (KKM/NIHSEC/P20-706).

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