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Research Article

JOURNAL OF PEDIATRICS, PERINATOLOGY AND CHILD HEALTH

ISSN: 2641-7405

Neonatal Outcome in Pregnant Women with Confirmed COVID-19 Infection during the Last Two Weeks of a Viable Pregnancy: A Retrospective Data Analysis

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Abstract

Background: Pregnant women are typically vulnerable to infectious diseases due to exaggerated disease manifestations and detrimental effects on their obstetric and neonatal outcomes. Previous studies have demonstrated that pregnant women with COVID-19 had similar clinical manifestations as nonpregnant women. However, there is not enough knowledge about the outcomes of neonates born to infected women although it has been reported that maternal pneumonia results in unfavorable obstetrical outcomes, including the premature rupture of membranes (PROM), intrauterine fetal demise (IUFD), intrauterine growth restriction (IUGR), and neonatal death. This retrospective study analyzes the clinical characteristics of all women with confirmed COVID-19 infection who gave birth in AWH, Qatar, as well as the possible adverse neonatal outcomes associated with maternal COVID-19 infection.

Objective: To identify adverse neonatal outcomes in mothers with confirmed COVID-19 infection during the last two weeks of a viable pregnancy.

Methods: This retrospective study included newborn babies born to mothers diagnosed with COVID-19 infection between 1 April 2021 and 23 May 2021 at AWH, Hamad Medical Corporation.

Data: Clinical characteristics, investigation results, and course of treatment were gathered from medical records for both mothers and babies.

Results: Out of 108 babies born to COVID-19-infected mothers, 47 (43.5%) were identified with adverse neonatal outcomes. Prematurity (28.7%), low birth weight (26%), respiratory distress (33.3%), and neonatal depression (8.3%) were the most commonly associated outcomes. Eight out of 108 babies (7.4%) tested positive for COVID-19, with 4.6% incidence of vertical transmission and 2.8% transient viremia. Using logistic regression analysis, maternal pneumonia and CT values were found to be statistically significant factors for premature delivery but were not significantly associated with neonatal infection. However, maternal ferritin levels significantly predicted neonatal positive PCR results.

Conclusion: Our data support the possibility of the intrauterine transmission of SARS-CoV-2 even in asymptomatic women. Studies with a larger number of subjects are recommended for identifying the biological mechanisms involved.

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Citation: Khalil Mohd Khalil Salameh, Rajesh Pattu Valappil, Anvar Paraparambil Vellamgot, Sarfrazul Abedin, Naser Abulgasim Elkabir, Esam Mohamed Elhadi Elhaji, Lina Hussain M Habboub, Samer Alhoyed. Neonatal Outcome in Pregnant Women with Confirmed COVID-19 Infection during the Last Two Weeks of a Viable Pregnancy: A Retrospective Data Analysis. Journal of Pediatrics, Perinatology and Child Health 6 (2022): 509-518.

Received: December 02, 2022
Accepted: December 14, 2022
Published: December 19, 2022

Dr. Salameh KMK et al., J Pediatr Perinatol Child Health 2022
DOI:10.26502/jppch.74050136

Introduction

The growing pandemic of coronavirus disease 2019 (COVID-19) has posed a new threat to all humans worldwide. Pregnant women are typically vulnerable to infectious diseases due to exaggerated disease manifestations and detrimental effects on their obstetric and neonatal outcomes [1]. Pregnant women are more susceptible to infections due to altered cell-mediated immune functions. The physiological and anatomical changes causing cardiopulmonary alternations in pregnant women further weaken their ability to compensate for respiratory disorders [2]. In addition, infections in mothers increase the risk of their unborn fetuses, mainly due to the immature innate and adaptive immune system. SARS (severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome) caused by other viruses from the coronavirus family were associated with poorer outcomes during pregnancy such as abortion, intrauterine fetal growth restriction, preterm delivery, and maternal mortality [3]. Pregnant women suffer from immunologic and physiologic changes, making them more susceptible to viral respiratory infections, such as respiratory syncytial virus, influenza virus, and SARS-CoV [4]. It is increasingly evident that COVID-19 infections in pregnant women are not more severe compared to that in age-matched women where symptoms are typically mild [5-11], and childbirth did not aggravate the course of the illness or chest computed tomography (CT) features of COVID-19 [12]. Several studies reported that maternal pneumonia causes unfavorable obstetrical outcomes including the premature rupture of membranes (PROM), intrauterine fetal demise (IUFD), intrauterine growth restriction (IUGR), and neonatal death [13,14]. However, there are limited data concerning this population infected with COVID-19. It is not well established whether COVID-19 could transmit vertically and increase the risk to the fetus and neonate. Considerable knowledge gaps exist regarding the impact of COVID-19 on different stages of pregnancy and its impact on fetuses as regards growth restriction, prematurity, and short- and long-term morbidities [15]. It is strongly recommended to collect case data rapidly and pool global data on the natural history of women affected by suspected COVID-19 or confirmed SARS-CoV-2 in pregnancy to identify the appropriate treatment and implement preventative strategies in the current and future outbreaks.

The following pregnancy and perinatal outcomes were observed in previous studies [16-18]: preterm birth (PTB: before 37-week gestation), preeclampsia (PE), preterm pre-labor rupture of membranes (pPROM), fetal growth restriction (FGR), miscarriage, cesarean mode of delivery, fetal distress (as defined by original authors), Apgar scores <7 at 5 minutes, neonatal asphyxia, admission to neonatal intensive care unit (NICU), perinatal death (including both stillbirth and neonatal death), and evidence of vertical transmission (defined as the presence of mother-to-child transmission in the antenatal or perinatal period) [16-18].

Analysis of the Timing of Mother-to-Child Transmission of SARS-CoV-2

Classification of mother-to-child transmission was assigned following the WHO criteria [13].

A. Intrauterine transmission of SARS-CoV-2 during the peripartum period is likely to occur (even if the neonate is asymptomatic) if there is evidence of both early exposure and persistence, that is, at least one item in each of the following three categories:

1. The mother being positive for SARS-CoV-2 between 14 days before birth and 2 days after birth.
2. Early exposure, with the virus being detected in any of the following:
   a. A swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) in the first 24 hours of life.
   b. Amniotic fluid.
   c. Umbilical cord blood.
   d. A neonatal blood sample in the first 24 hours of life.
3. A swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) being positive after 24 hours of postnatal life.

B. Intrapartum or early postnatal transmission of SARS-CoV-2 is likely to occur (even if the neonate is asymptomatic) if there is a lack of evidence of in-utero exposure and evidence of intrapartum or early postnatal transmission, that is, at least one item in each of the following three categories:

1. The mother or another person in close contact with the baby being positive for SARS-CoV-2 between 14 days before birth and 2 days after birth.
2. Early exposure, with a swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) in the first 24 hours of life being negative.
3. Persistence: either of the following:

a. A swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) being positive between 24 hours and 2 weeks of postnatal life.

b. The neonate having a positive SARS-CoV-2 IgM assay in the first 2 to 3 weeks of postnatal life.

C. Superficial exposure to SARS-CoV-2 or transient viremia is likely to occur if the neonate is asymptomatic and at least one item in each of the following three categories is met:

1. The mother being positive for SARS-CoV-2 between 14 days before birth and 2 days after birth.
2. Early exposure, with the virus being detected in any of the following:

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a. A swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) in the first 24 hours of life.

b. Amniotic fluid.

c. Umbilical cord blood.

d. A neonatal blood sample in the first 24 hours of life.

3. No evidence of persistence or immune response, with a swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) being negative between 24 and 48 hours of life.

This retrospective study analyzed the maternal and neonatal clinical characteristics of women with confirmed COVID-19 infection during the last two weeks of a viable pregnancy who gave birth in AWH or transferred from other hospitals in Qatar. Their clinical data were collected for assessing the neonatal outcomes associated with maternal COVID-19 disease.

Methods and Materials

This retrospective chart review included newborn babies born to mothers with confirmed COVID-19 between 1 April 2021 and 23 May 2021 in AWH, Hamad Medical Corporation

.Maternal Data: For mothers, maternal parity (primiparous or multiparous), medical history records (fever, cough, shortness of breath, diarrhea, and vomiting), laboratory tests, COVID-19 PCR results with CT values, medication used, use of mechanical ventilation, and intensive care unit (ICU) admission were collected. Laboratory tests included routine antenatal blood tests including CBC, C-reactive protein (CRP), and serum ferritin level. For all women, we registered pregnancy outcomes, that is, gestational age at delivery, mode of delivery, and occurrence of the gestational hypertensive disorder, gestational diabetes mellitus, premature rupture of membranes, and fetal distress.

Neonatal Data: The neonatal data collected included sex, birth weight, 1- and 5-minute Apgar scores, cord blood gas Ph, neonatal ICU (NICU) admission, fever, respiratory distress, and level of respiratory support. The laboratory data collected comprised routine blood tests, including CBC, CRP, biochemical indicators of hepatic and renal function, blood culture, and COVID-19 RTPCR results with CT values, as well as chest X-ray findings. Other data included medication history, discharge diagnosis, and length of stay in the NICU.

SARS-CoV-2 Testing: Maternal and neonatal throat swabs and nasopharyngeal swabs were gathered and tested for SARS-CoV-2 RNA through the use of quantitative real-time PCR (qRT-PCR) technology and hydrolysis probe technology (the New Coronavirus 2019 Nucleic Acid Detection Kit [Dual Fluorescence PCR]) (19-21). Sample collection, processing, and laboratory testing followed guidance from the World Health Organization (22).

Data Collection and Confidentiality

Data were extracted from our electronic documentation system, Cerner software, and Collected in an excel sheet. There was no interaction with human subjects, and the identity of the research subjects was not revealed. A code was provided to each patient, and all codes were protected in a computer. The link between code and identifiers was destroyed at the end of the study, and the data will be stored in a locker for five years. The principal investigator can only access this data, and subject identifiers will not be shared outside HMC.

The current study was carried out in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and following the laws and regulations of MOPH (Ministry of Public Health) in Qatar. The study was conducted after obtaining approval from the institutional review board and ethical committee of the Medical Research Center, HMC, Qatar. The protocol number was MRC-01-21-756. This was a retrospective data collection, and no subjects were recruited for the study; thus, informed consent was not needed, and this was waivered by the institutional review board and ethical committee.

STROBE guidelines were utilized for reporting this study.

Statistical Consideration and Data Analysis

Anonymous data were collected and entered into a standard electronic database designed because of the study design and objectives. Descriptive statistics were utilized for summarizing all demographic, laboratory, clinical, and other characteristics of the patients and their mothers. The data and results were reported with median and range/mean and standard deviation or frequencies and percentages. The primary outcome variable is the incidence of vertical transmission of COVID-19 infection. This was estimated and tested through the use of the chi-square ($\chi 2$) test or the Fisher exact test as appropriate. Associations between two or more qualitative variables were evaluated using the chi-square ($\chi 2$) test or Fisher exact test. The mean of quantitative variables between two independent groups were analyzed through the use of the unpaired t-test or mann whitney U test as appropriate.

The relationship between maternal COVID-19 and prematurity, neonatal depression, and respiratory distress was estimated by deriving adjusted odds ratios (ORs) and confidence intervals from logistic regression models. All P values presented will be two-tailed, and P values <0.05 were considered statistically significant. All statistical analyses were performed using statistical packages SPSS 22.0 (SPSS Inc., Chicago, IL) and Epi-info (Centers for Disease Control and Prevention, Atlanta, GA) software.

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DOI:10.26502/jppch.74050136

Observations and Results

The present review included newborns born to COVID-19-infected mothers between 1 April 2021 and 23 May 2021 at AWH, Hamad Medical Corporation, Qatar. A total of 104 pregnant women with COVID-19 were assessed during this study period. 108 babies delivered to them (100 singleton delivery and 4 twin delivery).

Clinical and Laboratory Manifestations of COVID-19-Infected Pregnant Females

Details regarding the clinical and laboratory characteristics of the participating mothers are presented in Table 1.

In the exposed group (women with COVID-19), the median maternal age was 33 years (range: 23–45 years), and the median gestational age at delivery was 38 weeks (range: 28–41 weeks). Of the 104 mothers, 25.9% (n=27) were diagnosed with COVID pneumonia, out of which 19.2% (n=20) needed respiratory support. Three required mechanical ventilation, five were on HFNC, and the rest were on nasal cannula or mask oxygen. 23 (22.1%) mothers received dexamethasone as part of COVID-19 treatment.

61.5% (n=64) of the mothers underwent LSCS, while 38.4% (n=40) underwent vaginal delivery. 6.7% (n=7) of the deliveries required instrumental assistance.

COVID CT values ranged from 10.5 to 36.2 (median 23.2). 59 (56.7%) mothers were symptomatic before delivery. High CRP values were observed with a median of 40 mg/liter (range: 1–308).

Clinical and Laboratory Manifestations of Neonates

Clinical and laboratory parameters of all neonates are given in Table 2, while clinical and laboratory parameters of neonates admitted to the NICU are presented in Table 3.

A total of 108 newborns (100 singletons and 4 twin pregnancies) were assessed during the period of the present study. The gestational age of newborn babies ranged from 28 to 41 weeks, out of which 31 (28.7%) were born prematurely. Low birth weight was observed in 29 (26.8%) babies and MSAF in 47 (43.5%) deliveries. Forty-seven babies (43.5%) needed NICU admission, out of which 36 (74.5%) were symptomatic upon admission.

Nine neonates (8.3%) were observed to have perinatal depression needing active resuscitation (positive pressure ventilation), three of whom required endotracheal intubation and mechanical ventilation. Abnormal cord pH (pH < 7.1) was noted in six babies, out of which 4 had a pH less than seven indicating severe acidosis.

Respiratory distress was the most common symptom accounting for 76.6% (36/47 babies) of admissions. 86% (31/36) needed respiratory support; two babies were on HFOV, seven babies required conventional ventilation, nine babies were on CPAP, and thirteen babies improved with oxygen support using nasal cannula. 29 (61.7%) received first-line antibiotics among symptomatic babies. The median length of stay in the NICU was four days, ranging from 12 hours to 39 days.

Laboratory testing for COVID-19 was conducted on 106 (98.1%) neonates by RT-PCR using nasopharyngeal and throat swabs. Eight newborns (7.4%) tested positive for COVID-19. Three of these initially positive babies (at less than 24 hours of age) turned negative on a repeat test done after 24 hours. The remaining 5 cases were positive at less than 24 hours of age and upon repeat testing after 24 hours. So out of 104 mothers with confirmed COVID-19 infections, we had 5 cases of intrauterine or vertical transmission and 3 cases of transient viremia or **superficial exposure to SARS-CoV-2.** All cases of vertical transmission were admitted in the NICU (10.6% of NICU admissions), out of which three babies were born full-term and two preterm (set of twins). Two preterm babies and two term babies were born by LSCS (due to fetal distress for the twins and one term baby while the second term baby was for breech presentation). All three full-term babies were born asymptomatic and were discharged in stable condition.

Of these five newborns who were diagnosed with vertical transmission of COVID-19, three mothers had COVID pneumonia requiring respiratory support in the form of HFNC and average CT values of 13–30. The onset of symptoms to the delivery duration ranged from 3 to 7 days.

Of the three cases with transient viremia, two babies were born by LSCS and one by spontaneous vaginal delivery. Two babies needed NICU admission, but the third one was in a postnatal ward with the mother. One mother had COVID pneumonia before delivery.

NICU Admission Risk with Different Maternal and Neonatal Parameters

NICU admission risk of neonates was assessed with various maternal and neonatal parameters (Table 4).

The association between maternal and baby factors with NICU admission was modeled. For the early model, ten predictors (birth weight, mother length of stay, mode of delivery, hydroxychloroquine, dexamethasone, respiratory support, highest CRP, pneumonia, MSAF, and completed gestational age) were selected due to their significance in the bivariate analysis, in addition to their perceived clinical relevance. Then, stepwise backward selection was performed until all remaining variables were significant at an α of 0.05. Data are presented as odds ratios with 95% confidence intervals. Among those ten predictors, two remained

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Table 1: Clinical and laboratory parameters of the mothers (104 mothers).

	Median (range)	Number (percentage)
Age (years)	33 (23–45)	
Gravida	3 (0–13)	
Para	2 (0–9)	
Gestational age (in weeks)	38 (28–41)	
Preterm delivery		31 (29.8%)
MSAF		47 (45.1%)
PET		19 (18.2%)
Gestation diabetes		33 (31.7%)
Pneumonia		27 (25.9%)
Respiratory support		20 (19.2%)
Max. resp. support Nasal cannula Mask oxygen HFNC Ventilation		 8 (7.7%) 4 (3.8%) 5 (4.8%) 3 (2.9%)
Duration of respiratory support, days	3 (0.04 to 114) needed in 20 mothers	
Dexamethasone		23 (22.1%)
Remdesivir		7 (6.7%)
Lopinavir		13 (12.5%)
Hydroxychloroquine		12 (11.5%)
Mode of delivery Vaginal LSCS		 40 (38.4 %) 64 (61.5%)
Instrument use		7 (6.7%)
Days before delivery first COVID +ve	-4 (-29 to 0)	
COVID CT value	23.2 (10.5 to 36.2)	
Onset of symptoms before delivery, days	-6 (-27 to 5) of 59 mothers	
Positive COVID to hospital admission, days	2 (0–87)	
Ferritin mcg/Liter	53 (2–2289) done in 67 mothers	
CRP mg/Liter	40 (1–308) done in 74 mothers	
Mothers' length of stay, days	4 (0.6 to 114)	
Mothers' readmission		3 (2.88%)

significant in the final model (Table 5): meconium-stained amniotic fluid and gestation age.

The association between maternal factors with positive COVID-19 PCR result in the baby was also modeled. For the early model, seven predictors (prematurity, maternal COVID CT value <30, duration of COVID positivity and delivery, mode of delivery, highest ferritin, highest CRP, and pneumonia) were chosen due to their perceived clinical significance. Then, stepwise backward selection was conducted until all remaining variables were significant at an α of 0.05. Data are presented as odds ratios with 95% confidence intervals. Among those seven predictors, one remained significant in the final model which was the maternal ferritin level (Table 6).

Next, the association between maternal factors and preterm delivery was analyzed. For the early model, five predictors (maternal COVID CT value <30, duration of COVID positivity and delivery, highest ferritin, highest CRP, and pneumonia) were selected due to their perceived clinical significance. Then, stepwise backward selection was conducted until all remaining variables were significant at an α of 0.05. Data are presented as odds ratios with 95% confidence intervals. Among those five predictors, two remained significant in the final model (Table 7): COVID CT value of more than 30 and maternal pneumonia.

Table 2: Neonatal parameters of babies born to COVID-19-positive mothers (108 neonates).

	Median (range)	Number (percentage)
Gestation age, weeks	38 (28–41)	
Prematurity		31 (28.7%)
Birth weight, grams	2967 (900 to 4470)	
Sex: Male Female		52 (48.1%) 56 (51.9%)
Resuscitation needed Positive pressure ventilation Intubation		9 (8.4%) 6 (5.6%) 3 (2.8%)
Apgar 1 minute	9 (1 to 9)	
Apgar 5 minutes	10 (6 to 10)	
Cord PH	7.29 (6.79 to 7.39) done in 38	
Base excess	-2.6 (-24 to 2.1) in 31	
NICU admission		47 (43.5%)
Age upon NICU admission, hours	0 (0 to 70) of 47	
Age of first symptom, hours	0 (0 to 28) of 35	
Age at first COVID test done, hours	24 (0 to 96)	
COVID test result: Not done Negative Inconclusive Positive		 2 (1.9%) 98 (90.7%) 2 (1.9%) 6 (5.6%)
COVID CT value	34.2 (18.8 to 42) of 6	
Timing of second COVID test, hours	48 (28 to 96) done in 27	

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Table 3: Clinical and laboratory parameters of neonates admitted to the NICU.

NICU admission=47 babies	Median (range)	Number (percentage)
Age at NICU admission, hours	0 (0 to 70)	
Symptomatic at admission		35/47 (74.5%)
Age at first symptom, hours	0 (0 to 28)	
Respiratory distress/ desaturation		36/47 (76.6%)
Respiratory support		31/47 (66%)
Maximum respiratory support Nasal cannula CPAP Ventilation MV/HFOV		13/47 (27.7%) 9/47 (19.1%) 7/47 (14.9%) 2/47 (4.2%)
Respiratory support duration, hours	24 (1 to 240)	
Antibiotics use		29/47 (61.7%)
Duration of antibiotics, days	2 (2–7)	
CRP mg/Liter	1.5 (1 to 40) done in 22	
WBC per cubic milli meter	12.5 (4.4 to 42.7) done in 37	
Age at first COVID test done, hours	22.5 (0 to 96)	
COVID CT value	34.2 (18.8 to 42) positive in 6	
Age at second COVID test done, hours	48 (28 to 96) done in 27	
NICU stay	4 days (12 hours to 39 days)	

Discussion

Main Findings

In the present study, out of the 104 women with confirmed COVID-19 infection, a positive RTPCR result was found in eight babies (7.4%). Out of the 108 newborns analyzed in the current study, five cases of intrauterine or vertical transmission and three cases of transient viremia or **superficial exposure to SARS-CoV-2 were detected.** These five neonates had no contact with infected patients, except for their mothers during delivery, indicating vertical and intrapartum transmission. Although not statistically significant, this provides convincing evidence for possible vertical transmission according to the WHO criteria for classifying the timing of mother-to-child transmission of SARS-CoV-2.

Vertical Transmission according to WHO Criteria

To identify instances of vertical transmission and classify peripartum transmission according to the classification proposed by Blumberg et al.23 and modified by the WHO24, we analyzed the detection timeline in cases with a positive neonatal SARS-CoV-2 test result. We considered the five cases with a persistent positive neonatal SARS-CoV-2 result after 24 hours (the neonate was positive both at birth and after 24 hours) to correspond to possible intrauterine transmission. Two of these neonates had persistent SARS-CoV-2 identification for more than three weeks. Furthermore, three neonates were identified as having transient viremia (unlikely intrauterine transmission) due to the non-persistence of SARS-CoV-2 RNA amplification 24 hours after birth. None of the cases were negative at birth but positive 24 hours after birth to categorize as having early postnatal transmission (intrapartum transmission).

Table 4: NICU admission risk with different maternal and neonatal parameters.

	NICU admission=47 Mean/no. %	No NICU admission= 61 Mean/no. %	Odds ratio (95% confidence interval)	Mean difference (95% confidence interval)	P value
Mothers' age, years	32.85	32.5		0.326 (-1.76 to 2.41)	0.757
Gravida	3.51	3.39		0.117 (-0.73 to 0.97)	0.786
Para	2.23	2.1		0.136 (-0.604 to 0.87)	0.717
MSAF	14/47 29.8%	5/61 8.2%	4.75 (1.56 to 14.38)		**0.003**
PET	7/47 14.9%	6/61 9.8%	1.6 (0.50 to 5.13)		0.423
Gestation diabetes	14/47 29.8%	19/61 31.1%	0.93 (0.41 to 2.14)		0.999
Pneumonia	19/47 40.4%	8/61 13.1%	4.49 (1.74 to 11.56)		**0.001**
Dexamethasone	15/47 31.9%	8/61 13.1%	3.1 (1.18 to 8.14)		**0.018**
Remdesivir	5/47 10.6%	2/61 3.3%	3.51 (0.65 to 18.97)		0.236
Lopinavir	7/47 14.9%	6/61 9.8%	1.6 (0.5 to 5.13)		0.553
Hydroxychloroquine	5/47 10.6%	7/61 11.5%	0.91 (0.27 to 3.1)		0.999
Vaginal LSCS	11/47 23.4% 36/47 76.6%	33/61 54.1% 28/61 49.9%	0.26 (0.11 to 0.6)		**0.001**
Respiratory support	14/47 29.8%	6/61 9.8%	3.88 (1.36 to 11.1)		**0.008**
Duration of respiratory support, days	13.7	4.5		9.24 (-17.02 to 35.5)	**0.469**

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Mothers' hospital stay, days	9.26	4.22		5.04 (0.6 to 9.4)	**0.026**
COVID CT value	22.9	24.2		-1.29 (-3.76 to 1.18)	0.304
The onset of symptoms before delivery, days	5.58	6.54		-0.963 (-3.59 to 1.66)	0.467
Days COVID test +ve before delivery	4.62	5.9		-1.36 (-3.42 to 0.69)	0.191
Positive COVID to hospital admission	2.81	5.51		-2.7 (-6.23 to 0.83)	0.133
Ferritin mcg/liter	261.4	138.1		123 (-59 to 305)	0.182
CRP mg/liter	77.8	47.3		30.4 (1.6 to 59.3)	**0.039**
Gestation age, week	35.8	38.1		-2.29 (-3.34 to -1.23)	**0.001**
Birth weight, gram	2655	3121		-466 (-731 to -200)	**0.001**
Male Female	23/47 48.9% 24/47 51.1%	29/61 47.5% 32/61 52.5%	1.05 (0.49 to 2.26)		0.886
Apgar 1 minute	7.38	9.0		-1.61 (-2.31 to -0.92)	**0.001**
Apgar 5 minutes	9.34	10		-0.66 (-0.94 to -0.38)	**0.001**
Cord pH	7.23	7.3		-0.072 (-0.23 to 0.09)	0.381
Base excess	-3.73	0.2		-3.93 (-11.19 to 3.32)	0.276
Baby COVID test Negative Inconclusive Positive	 39/47 83% 1/47 2.1% 6/47 12.8%	 59/61 96.7% 1/61 1.6% 0/61 0%			**0.038**

Table 5: Multivariable logistic regression equations predicting NICU admission using variables from maternal and baby parameters.

Variable	Odds ratio	95% confidence interval	P value
MSAF	29.4	2.63 to 333.3	0.006
Gestational age	0.649	0.488 to 0.853	0.002

Table 6: Multivariable logistic regression equations predicting positive COVID-19 PCR result in the baby using variables from maternal parameters.

Variable	Odds ratio	95% confidence interval	P value
Maternal ferritin level	1.004	1.001 to 1.006	0.009

Table 7: Multivariable logistic regression analysis predicting prematurity using variables from maternal parameters.

Variable	Odds ratio	95% confidence interval	P value
Maternal COVID CT value <30	0.32	0.096 to 1.068	0.064
Pneumonia	5.07	1.65 to 15.62	0.005

Persistence of viremia was observed in a set of twin preterm babies, and in these cases, the mother was symptomatic and had PPROM for 24 hours. We may not be able to establish a relationship between PPROM and persistent viremia from this case. However, more observations are needed to prove this issue.

We also found that all five positive cases with intrauterine transmission were female babies. The female sex could be a risk factor for vertical transmission.

Our findings were in agreement with reports demonstrating that most SARS-CoV-2-positive pregnant women are asymptomatic or have a mild disease (25–27). 25% of mothers had respiratory symptoms and were diagnosed with COVID pneumonia and 18% needed respiratory support. Interestingly, most of the neonates positive for SARS-COV-2 were born to symptomatic mothers (mainly respiratory). Out of the five positive newborns, three full-term babies were asymptomatic, while the remaining two were born preterm and symptomatic requiring respiratory support. However, we cannot exclude the fact that symptoms could be related to other conditions (28) such as HMD of prematurity.

The time needed for SARS-CoV-2 to cross the placenta into the AF and cause intrauterine infection remains unknown. For other viruses, such as the herpes simplex virus, neonates born to mothers infected from 5 days before to 2 days after delivery might develop an infection (29). It is not always possible to accurately determine the timing of maternal infection, especially in asymptomatic women (30). Animal models reveal that cytomegalovirus reaches the placenta and infects the fetus 7 and 14 days after infection, respectively (31). For arboviruses, viral RNA is detected in the placenta and fetus 4 days after infection (32).

Some studies have reported the presence of SARS-CoV-2 in the placenta of women infected 4 to 17 days before delivery (28, 34). It is worth mentioning that the majority of women

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DOI:10.26502/jppch.74050136

remained asymptomatic in this study population, which makes determining the timing of infection difficult. Evidence supports that SARS-CoV-2 can replicate in the placenta and reach the AF despite the controversy. However, the timeline for this event is not clear (35). Prospective studies are required for determining the length of time that the virus needs to cross the placenta and infect the fetus.

Numerous studies have investigated whether the viral load is associated with disease severity or infectiousness (36), with a higher viral load found in critically ill patients in comparison with asymptomatic patients or those with mild disease (37). We investigated seven predictors (prematurity, maternal COVID CT value less than 30, duration of COVID positivity and delivery, mode of delivery, highest ferritin, highest CRP, and pneumonia) as factors influencing intrauterine transmission. Among those factors, only the ferritin level was found to be statistically significant. No difference was observed when assessing maternal CT values according to whether the neonatal swabs were positive or negative.

Out of the five predictors analyzed as risk factors for premature delivery (maternal COVID CT value >30, duration of COVID positivity and delivery, highest ferritin, highest CRP, and pneumonia), two remained significant, that is, CT value less than 30 and maternal pneumonia.

A point of strength of the present study is the improved neonatal detection rate of SARS-CoV-2 by collecting two different samples. However, the study has possible limitations, including the inability to both identify the timing of maternal infection and test the amniotic fluid samples.

To sum up, our data support the possibility of intrauterine transmission of SARS-CoV-2 even in asymptomatic women. Studies with a larger number of subjects are recommended for determining the biological mechanisms involved.

Declarations

Ethics approval and consent to participate: The current study was carried out in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and following the laws and regulations of MOPH (Ministry of Public Health) in Qatar. The study was conducted after obtaining approval from the institutional review board and ethical committee of the Medical Research Center, HMC, Qatar. The protocol number was MRC-01-21-756. This was a retrospective data collection, and no subjects were recruited for the study; thus, informed consent was not needed, and this was waivered by the institutional review board and ethical committee.

Consent for publication: No need for this research as no identity disclosure has been done in this manuscript.

Availability of data and materials

It will be provided as per request from journal.

Competing interests

There are no conflicts of interest in this work to declare. No conflict of interest among authors.

Funding

No funding was taken for this study. Once accepted for publication then we can request publication money from Qatar national foundation, Qatar.

Authors contirbutions

K.S-Design of study,formulating research questions, R.P-writng and editing drafts,data collection,writing of manuscript, A.P-Data collection, analysis, S.A-review, analysis and proof reading of manuscripts, NA-data collection, EM-data collection, Dr. L.H-coceptulization,review data, S.A.L -data collection.

The author(s) read and approved the final manuscript.

Acknowledgements

NIL

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Abbreviations and Acronyms

SARS-CoV-2 testing: Maternal and neonatal nasal and throat swabs collected and tested for SARS-CoV-2 RNA using quantitative real-time PCR (qRT-PCR) technology and hydrolysis probe technology (the New Coronavirus 2019 Nucleic Acid Detection Kit [Dual Fluorescence PCR])

Confirmed COVID-19 infection:

Defined as nasal and throat swabs positive for SARS-CoV-2 RNA using quantitative real-time PCR (qRT-PCR)

Adverse Neonatal outcomes

Defined as outcomes including prematurity, Intrauterine growth retardation, respiratory distress, neonatal depression, and perinatal asphyxia

Viable pregnancy

Pregnancy with gestational age of more than 24 weeks

NICU: Neonatal intensive care unit

LSCS: Lower segment caesarian section

SVD: Spontaneous vaginal delivery

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DOI:10.26502/jppch.74050136

TTN: Transient tachypnea of newborn

HMC: Hamad Medical Corporation

AWH: Al-Wakra Hospital

HFOV: High frequency oscillatory ventilation

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Citation: Khalil Mohd Khalil Salameh, Rajesh Pattu Valappil, Anvar Paraparambil Vellamgot, Sarfrazul Abedin, Naser Abulgasim Elkabir, Esam Mohamed Elhadi Elhaji, Lina Hussain M Habboub, Samer Alhoyed. Neonatal Outcome in Pregnant Women with Confirmed COVID-19 Infection during the Last Two Weeks of a Viable Pregnancy: A Retrospective Data Analysis. Journal of Pediatrics, Perinatology and Child Health 6 (2022): 509-518.

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Citation: Khalil Mohd Khalil Salameh, Rajesh Pattu Valappil, Anvar Paraparambil Vellamgot, Sarfrazul Abedin, Naser Abulgasim Elkabir, Esam Mohamed Elhadi Elhaji, Lina Hussain M Habboub, Samer Alhoyed. Neonatal Outcome in Pregnant Women with Confirmed COVID-19 Infection during the Last Two Weeks of a Viable Pregnancy: A Retrospective Data Analysis. Journal of Pediatrics, Perinatology and Child Health 6 (2022): 509-518.