Friday, October 21, 2022
12:15 PM – 1:30 PM
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CLINICAL CHARACTERISTICS AND VERTICAL TRANSMISSION OF PREGNANT WOMEN WITH SARS-CoV-2 INFECTION AND THEIR NEONATES

Jiyoung Lee[1], Mi-young, Lee[2], Eui-seok, Jung[3], Ji-na, Lee[4], Seongman Bae[1], Jiwon Jung[1], Min-jae, Kim[1], Young-pill, Chong[1], Sang-oh, Lee[1], Sang-ho, Choi[1], Yang-soo, Kim[1], Sung-Han Kim[1]

[1]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea,
[2]Department of Obstetrics and Gynecology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea,
[3]Department of Neonatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea,
[4]Department of Pediatric Infectious Disease, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Contact information
Sung-Han Kim, MD, PhD
Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul,
Republic of Korea
Tel: +82-2-3010-3305, E-mail: kimsunghanmd@hotmail.com

REVISED ABSTRACT

Background: There are limited data on the clinical characteristics and the vertical transmission rate of pregnant women with severe acute respiratory syndrome coronavirus infection and their neonates in South Korea.

Methods: Pregnant women who tested positive for severe acute respiratory syndrome corona virus 2 infection were retrospectively reviewed in Asan Medical Center from September 1, 2020, to April 26, 2022. All neonates and infected women underwent a polymerase chain reaction test for severe acute respiratory syndrome corona virus 2 within 24 hours of birth and at 48-hour interval if they stayed in the hospital.

Results: A total of 60 pregnant women gave birth by cesarean section (n=40, 67%) or vaginal delivery (n=20, 33%). Among them, 3 women gave birth to twins. Delivery occurred, on average, at 38+2 weeks (± 2^{+0}) of gestational age, and 9 patients (15%) had underlying diseases. Of these 60 patients, 9 (15%) received coronavirus disease 2019 vaccinations. Pneumonia was confirmed by a chest radiograph in 7 patients (12%), and 2 patients (3%) required supplemental oxygen therapy, both of whom eventually recovered. The mean birthweight of the neonates was 3137 g (± 558). Further, 8 neonates (13%) were of low-birth weight (< 2500 g), and 11 neonates (17.5%) were preterm (<37 weeks of gestation). Apgar score was median 8 (8 - 9) at 1 minute and 9 (9 – 9.5) at 5 minutes. Four neonates (6.3%) required invasive mechanical ventilation. All neonates had negative severe acute respiratory syndrome corona virus 2 test results. Therefore, there was no vertical transmission in 63 of the neonates (0%, 95% CI 0-6)

Conclusion: Pregnant Korean women with severe acute respiratory syndrome coronavirus 2 infection had favorable obstetric outcomes, and the risk of vertical transmission to their neonates was low. Managing the infection risks of pregnant women and their neonates during the coronavirus disease 2019 pandemic are required.

INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, China.[1] Since then, the coronavirus disease 2019 (COVID-19) pandemic has affected various vulnerable populations. Given that pregnant women infected with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have a poor prognosis and there are limited data on their vertical infection, [2,3] several previous studies investigated whether pregnant women infected with SARS-CoV-2 had a poor prognosis and whether it could cause vertical transmission.[4,5] A meta-analysis conducted in 2020 reported that pregnant women with SARS-CoV-2 infection had a poor prognosis.[4] A recent multicenter cohort study in 2021 revealed that the prevalence of SARS-CoV-2 infection in neonates born from pregnant women with SARS-CoV-2 infection was approximately 2%.[5] However, there are limited data on the clinical characteristics of pregnant women with SARS-CoV-2 infection and their neonates, and the vertical transmission rate in South Korea. In this study, we investigated the clinical characteristics of pregnant women with SARS-CoV-2 infection and the vertical transmission to their neonates.

METHODS

All pregnant women who were confirmed to have SARS-CoV-2 infection and were admitted for delivery were retrospectively reviewed at Asan Medical Center, Seoul, South Korea, from September 1, 2020, to April 26, 2022. All neonates of the SARS-CoV-2-infected women were tested with a nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test within 24 hours of birth and at 48-hour interval if the neonates in the hospital. During the hospitalization period after delivery, rooming-in system were not applied. Parents and guardians, including SARS-CoV-2 confirmed mothers, were not permitted to visit the newborn. Breastfeeding was not performed, and disposable bottle feeding was performed. All maternal and neonate data were collected from electronic medical records. This cohort study was approved by our Institutional Review Board of the Asan Medical Center(No. AMC-2022-0625). Needs for the written informed consent was waived.

Statistical analysis was performed with SPSS, (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Vertical transmission rate was analyzed by the modified Wald method and 95% confidence intervals were calculated.

RESULTS

Sixty pregnant women who delivered 63 live newborns (57 singletons and 3 pairs of twins) from September 1, 2020, to April 26, 2022, were included in the study. Maternal demographic and clinical characteristics are presented in Table 1. The women gave birth by cesarean section (n=40, 67%) or vaginal delivery (n=20, 33%). The mean (± standard deviation [SD]) maternal age was 34 (± 4.7) years. Delivery was performed at a mean gestational age of 38+2 weeks (± 2+0), and 9 patients (15%) had underlying diseases. Diabetes was the most common underlying disease (n=4, 13%). Among them, three patients were gestational diabetes mellitus and one patient was type 1 diabetes mellitus. The median (interquartile range [IQR]1 – IQR3) number of days from the date of diagnosis of SARS-CoV-2 infection to delivery was 1 (0 - 3). Of these 60 patients, 9 (15%) received COVID-19 vaccinations. Among them, there were two patients (3.3%) who completed up to the third inoculation. There were 48 (80%) women who were asymptomatic or had mild illness. Pneumonia was confirmed by chest radiographs in 7 patients (12%), and 2 patients (3%) required supplemental oxygen therapy and eventually recovered. Of the clinical symptoms, pregnant women with SARS-CoV-2 infection commonly presented with cough (n=21, 35%) at admission. One woman had a delivery-related complication. After cesarean section, active bleeding was confirmed, and embolization and open surgery were performed. There were 10 (17%) women who received monoclonal antibody, such as regdanvimab, for the treatment of post-partum COVID-19 complications.

Neonatal demographic and clinical characteristics are shown in Table 2. The mean weight (± SD) of newborns was 3137 g (± 558), of which 8 neonates (13%) were considered to be of a low-birth weight (< 2500 g), and 11 neonates (17.5%) were born prematurely ((<37 weeks of gestation). Preterm delivery occurred, on average, at 35+0 weeks (± 2+0) of gestational age, The causes of premature delivery were premature rupture of membranes, preterm labor, twin, vaginal bleeding, and worsening of pregnant women due to preeclampsia. There was no case of premature delivery due to the deterioration of the mother's condition due to SARS-CoV-2 infection. Median Apgar score (IQR1 – IQR3) was 8 (8-9) at 1 minute and 9 (9-9.5) at 5 minutes. 21 of them (33.3%) required oxygen supplement, 1 (1.6%) required neonatal resuscitation with positive pressure ventilation, and 2 (3.2%) required endotracheal intubation in delivery room. Five neonates (8%) required mechanical ventilation including Continuous Positive Airway Pressure (CPAP) in neonatal intensive care unit, four of whom eventually recovered. Among them, four neonates (6.3%) required invasive mechanical ventilation. Their gestational age at birth, birthweight, reasons for using mechanical ventilation(including CPAP), period of use of mechanical ventilation are summarized in Table 3. All neonates exhibited negative SARS-CoV-2 PCR results within 24 hours of birth. All 45 newborns who underwent the SARS-CoV-2 PCR test at 48 hours after birth were confirmed to be negative. In the case of a long stay of the newborn after 48 hours, SARS-CoV-2 PCR test was performed on the 7th and 14th days, but it was confirmed to be negative. Thus, there was no vertical transmission in any of the 63 neonates (0%, 95% confidence interval [CI] 0-6).

Table 1. Maternal Characteristics

Variable			n (%)	Variable			n (%)
Age (year), mean (SD)			34 (± 4.7)	Elevated LD (> 250 IU/L)		Yes	16 (56.7)
Period	Pre-delta (Sep 2020 – May 2021)		1 (1.7)			No	34 (26.7)
	Delta (June 2021 – Jan 2022)		13 (21.7)			Unchecked	10 (16.7)
	Omicron (Feb 2022 – Apr 2022)		46 (76.7)	Symptom	Any symptom		37 (61.7)
Gestational age (weeks), mean (SD)			38^{+2} (± 2^{+0})		Fever		18 (70.0)
Period between first positive SARS-CoV-2 test and delivery (day), median (IQR)			1 (0-3)		Chill		6 (10.0)
Birth-related complications			1 (1.7)		Cough		21 (35.0)
Method of Delivery	Cesarean section		40 (66.7)		Sputum		9 (15.0)
	Vaginal delivery		20 (33.3)		Sore throat		13 (21.7)
Vaccination	Yes		9 (15.0)		Dyspnea		3 (5.0)
	No		33 (55.0)		Rhinorrhea		4 (6.7)
	Unknown		18 (30.0)		Myalgia		6 (10.0)
Underlying Disease	Any disease		9 (15.0)		Headache		7 (11.7)
	DM		4 (13.3)		Nasal congestion		3 (5.0)
	Solid cancer		2 (3.3)		Hyposmia		1 (1.7)
	Cardiovascular disease		2 (3.3)		Hypogeusia		1 (1.7)
	HTN		1 (1.7)	NIH severity	1. Asymptomatic		23 (38.3)
Pneumonia			7 (11.7)		2. Mild illness		25 (41.7)
Lymphocyte count, mean (SD)			1208 (± 553.5)		3. Moderate illness		10 (26.1)
Lymphocytopenia (<1000)	Yes		16 (26.7)		4. Severe illness		2 (5.2)
	No		22 (36.7)		5. Critical illness		0 (0.0)
	Unchecked		22 (36.7)	Treatment	Regdanvimab		10 (16.7)
CRP (mg/dL), mean (SD)			0.94 (± 0.76)		Dexamethasone		1 (1.7)
Elevated CRP (>0.6 mg/dL)	Yes		30 (50.0)		Remdesivir		1 (1.7)
	No		27(45.0)	O2 supply			2 (3.3)
	Unchecked		3 (5.0)	ICU care			0 (0.0)
				Mechanical ventilation			0 (0.0)
				In hospital mortality			0 (0.0)

SD, standard deviation; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; C/sec, caesarean section; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; NIH, National institutes of health

Table 2. Neonatal Characteristics

Variable			n (%)	Variable			n (%)
Sex	Male		37 (58.7)	Delivery room management	Oxygen supply		21 (33.3)
	Female		26 (41.3)		Positive pressure ventilation		1 (1.6)
Gestational age (weeks), mean (SD)			38^{+2} (± 2^{+0})		Endotracheal intubation		2 (3.2)
Birthweight(g), mean (SD)			3137 (± 557.6)		Cardiac compression		0 (0.0)
Low birthweight (<2500g)			8 (12.7)		Epinephrine administration		0 (0.0)
Preterm birth (<37 weeks)			11 (17.5)	SARS-CoV-2 PCR (positive)	1st (n=63)		0 (0.0)
Small for gestational age			14 (22.2)		2nd (n=45)		0 (0.0)
Apgar score median (IQR)	1 min		8 (8-9)	Vertical transmission			0 (0.0)
	5 min		9 (9-9.5)	Mechanical ventilation	Invasive		4 (6.3)
Mortality			0 (0.0)		Non-invasive		1 (1.6)

SD, standard deviation; IQR, Interquartile range

Table 3. Characteristics of Neonates Requiring Mechanical Ventilation

	Neonate 1	Neonate 2	Neonate 3	Neonate 4	Neonate 5
Gestational age (weeks+days)	34+4	39+0	40+1	29+2	34+1
Birthweight (g)	2930	3560	2930	1180	2600
Reasons for using mechanical ventilation	Respiratory distress syndrome	Not breathing at birth	Absent pulmonary valve syndrome, ventricular septal defect	Respiratory distress syndrome	Transient tachypnea of the newborn
Period of use of mechanical ventilation including CPAP (day)	7	3	29	63[a]	2

CPAP, Continuous positive airway pressure
[a]Currently hospitalized and CPAP applied state.

DISCUSSION

One previous study demonstrated the transplacental transmission of SARS-CoV-2 in a neonate born from a mother with SARS-CoV-2 infection.[6] The transmission was confirmed by virological and pathological investigations of samples of the mother and neonate's blood, and the placenta.[6] Another study analyzed the viral genome of pregnant women with SARS-CoV-2 infection and their neonates with nasopharyngeal swabs, vaginal swabs, maternal and umbilical cord plasma, placenta and umbilical cord biopsies, amniotic fluids and milk.[7] They detected the SARS-CoV-2 genome in umbilical cord blood, the placenta, vaginal mucosa, milk specimen.[7] These studies suggest that vertical transmission can occur. However, most studies on the vertical transmission of SARS-CoV-2 in clinical practice were based on case reports or small case series.[8-13] According to a recent prospective multicenter cohort study, among the 36 neonates in which nasopharyngeal swabs were taken, only 1 neonate (3%, 95% CI 0.1 - 15) had a positive PCR result. IgM was not detected in cord blood.[14] According to a study of 34 newborns conducted in south Korea, vertical transmission was not confirmed.[15] However, all of these studies have a limitation in that the number of study subjects was small. For this reason, several systematic reviews were conducted. According to a systematic review, no clear evidence for vertical transmission of SARS-CoV-2 has been suggested from the available literature.[16] According to another systematic review study, vertical transmission was possible; however, it was unclear whether SARS-CoV-2 positive neonates were infected in utero, intrapartum or postpartum.[17] A more recent multicenter cohort study investigating 255 neonates, reported SARS-CoV-2 infection in 2% of neonates.[5] In contrast, in a recent retrospective study of 101 newborns in New York, no clinical evidence of vertical transmission was identified.[18] The results of this study suggest that the risk of vertical transmission in practice was not high. Our study is also consistent with these New York data. The data on the probability of vertical transmission provide important information for managing the healthcare system during childbirth and newborn care as outbreaks, such as those caused by the omicron variant, exacerbate the pandemic.[19] Although it may be ideal to care for newborns in an appropriate isolation facility and deliver in a negative pressure operating room, when the medical system is overloaded, a lack of resources makes it difficult to provide the appropriate facilities, thus clinicians should consider the risk of vertical transmission while distributing these resources. In this respect, our data provide important scientific evidence for Korea disease control and prevention agency's policy to allow childbirth in general obstetric rooms during the omicron pandemic period.

According to a systematic review, pregnant women with COVID-19 were less likely to manifest symptoms such as fever, dyspnea, and myalgia, more likely to be admitted to an intensive care unit or need invasive ventilation, more likely to deliver prematurely, have an increased risk of maternal death. and The neonates were more likely to be admitted to the neonatal unit.[4] A recent study of 6,012, SARS-CoV-2 infected pregnant women in Canada also reported that the hospitalization rate, intensive care unit admission rate, and the preterm birth rate were higher in pregnant women with COVID-19 than in non-pregnant women with COVID-19.[20] In contrast, according to a systematic review, although the majority of mothers were discharged without any major complications, severe maternal morbidity as a result of SARS-CoV-2 infection and perinatal death were reported.[16] Another systematic review also reported that severe and critical disease in pregnant women with COVID-19 were similar to that in general population.[17] In our study, most pregnant women who were about to give birth experienced mild illness despite low vaccination rate. This discrepancy between studies might stem from the different gestation age and the different stages of the COVID-19 pandemic that could affect COVID-19 treatment, vaccination status, and the dominance of SARS-CoV-2 variants. Therefore, although most unvaccinated pregnant Korean women who were about to give birth had favorable outcomes during the omicron-dominant period, COVID-19 vaccination in pregnant women cannot be overemphasized because of complications during delivery in SARS-CoV-2-infected pregnant women and the concern of the emergence of new variants.

In delivery, the participation of a health care provider who is sufficiently trained in neonatal resuscitation is essential. A multidisciplinary approach, including a neonatologist, was recommended for neonatal resuscitation according to guidelines early in the COVID-19 pandemic.[21] Wearing all personal protective equipment, they participated in the delivery process of COVID-19 positive mothers, which may or may not require resuscitation of the newborn. However, the lack of medical resources brought about by the Omicron pandemic has made it laborious to provide adequate resuscitation to newborns born to all COVID-19 mothers. The number of neonates receiving positive pressure ventilation or intubation reported in this study was 3(4.8)%, which was not higher than the 6% reported in other literature.[22] Therefore, our report can be influential for efficiently allocating medical resources during a pandemic.

In this study, the median number of day from the date of diagnosis of SARS-CoV-2 infection to delivery was 1 (0 - 3). Most of the pregnant women included in this study were hospitalized due to symptoms related to delivery such as labor pain or premature rupture of membrane while performing self-isolation after being diagnosed with SARS-CoV-2 infection in the full term state, so the median day was short. However, there were 12 cases that took more than 4 days from SARS-CoV-2 infection to delivery, and the fact that vertical transmission did not occur among them can be considered as meaningful data.

This study has some limitations. We could not determine the exact timing of maternal infection, especially in pregnant women with asymptomatic SARS-CoV-2 infection. Since all maternal and neonate data were collected retrospectively through electronic medical records, the prognosis of the mother and the newborn could not be confirmed after discharge. Moreover, our results may not be generalized as it is a single center study. Further, this study could not have a large sample size. It is necessary to investigate with a large sample size whether vertical transmission occurs with SARS-CoV-2 infection. Future studies should analyze prognosis by comparing pregnant women with and without SARS-CoV-2 infection. Additional genetic and pathological studies by collecting placenta and blood samples of the mother with SARS-CoV-2 infection and blood samples of the newborn may also be helpful to study vertical transmission further.

In conclusion, although the literature is limited in its understanding of pregnant women with SARS-CoV-2 infection, our study revealed that obstetric outcomes were favorable. Managing the risks associated with infection of pregnant women and their neonates during the COVID-19 pandemic should be considered.

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