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Clinical Characteristics and Risk of Hypoxemia Development in Women Infected with SARS-CoV-2 during Pregnancy

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Purpose: There is limited information on the clinical characteristics and prognosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy. The clinical features and risk factors for hypoxemia development were investigated in pregnant women with coronavirus disease-2019 (COVID-19).

Materials and Methods: From August 2020 to February 2022, we performed a retrospective cohort study of 410 pregnant women with COVID-19. The clinical characteristics and prognoses were compared between pregnant COVID-19 patients requiring oxygen and those who did not.

Results: Of 410 patients, 100 (24.4%) required oxygen therapy. Among them, fever [163 (52.6%) vs. 81 (81.0%), p<0.001] and cough [172 (56.4%) vs. 73 (73.0%), p=0.003] were more frequently observed than in non-oxygen group. The proportion of unvaccinated women was higher in oxygen group than in non-oxygen group [264 (85.2%) vs. 98 (98.0%), p=0.003]. During the Omicron wave, patients were more likely to have no oxygen requirement [98 (31.6%) vs. 18 (18.0%), p=0.009]. The risk of hypoxemic respiratory difficulty increased if SARS-CoV-2 infection occurred during the third trimester [adjusted odds ratio (aOR) 5.083, 95% confidence interval (CI): 1.095–23.593, p=0.038] and C-reactive protein (CRP) was elevated (≥1.0 mg/dL) at admission (aOR 5.878, 95% CI: 3.099–11.146, p<0.001). The risk was higher in unvaccinated patients (aOR 5.376, 95% CI: 1.193-24.390, p=0.028). However, the risk was lower in patients during the Omicron wave (aOR 0.498, 95% CI: 0.258–0.961, p=0.038).

Conclusion: A quarter of SARS-CoV-2-infected women developed hypoxemic respiratory difficulty during pregnancy. SARS-CoV-2 infection during the third trimester, CRP elevation at admission, and no vaccination increased the risk of hypoxemia in pregnant women.

Key Words: Pregnancy, COVID-19, severe acute respiratory syndrome coronavirus 2, risk factors, Severity of Illness Index

INTRODUCTION

In the early days of the coronavirus disease-2019 (COVID-19) pandemic, pregnant women faced uncertain risks associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, ranging in severity from asymptomatic to critical.[1,2] Fever and hypoxemia during pregnancy may increase the risk of intrauterine growth restriction, premature delivery, malformations, and stillbirth. Social factors, such as limited access to care and difficulties with social isolation, may negatively impact maternal and fetal outcomes.[3,4]

During pregnancy, several guidelines recommend maintaining O_2 saturation (SpO_2) above 95% to accommodate the phys-

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iologic changes in oxygen demand and to ensure adequate oxygen delivery to the fetus. Persistent hypoxemia causes intrauterine growth restriction, leading to fetal distress and increasing the risk of preterm birth.[5,6]

Several studies reported that pregnant women are at increased risk of severe clinical presentation of COVID-19, such as admission to the intensive care unit, the need for mechanical ventilation, and death.[7-10] However, it was reported that the risk of severe disease and mortality due to COVID-19 did not differ between pregnant and non-pregnant women of childbearing age in the same age group.[11] Previous studies included either cases of confirmed COVID-19 during hospital admission for obstetric delivery or highly heterogeneous cases. Therefore, they may not adequately represent the full effect of SARS-CoV-2 on the pregnant populations, including infection acquired at any point of pregnancy and the range of disease severity.

Evidence of poor maternal outcomes from past outbreaks of viral respiratory disease, such as severe acute respiratory syndrome (SARS),[12,13] Middle East respiratory syndrome (MERS),[14] and 2009 influenza (H1N1),[15,16] suggests that SARS-CoV-2 also differentially affects pregnant women. However, international data have varied in the degree of illness severity resulting from SARS-CoV-2 infection.[7,17-19] Until February 2022, all pregnant women with SARS-CoV-2 infection in South Korea were hospitalized after laboratory confirmation with real-time reverse transcription polymerase chain reaction (RT-PCR). COVID-19 was relatively well-controlled in South Korea regarding the number of cases and severity; therefore, adequate information about pregnant women with COVID-19 could be obtained up to February 2022. In catastrophic medical situations such as COVID-19, it is necessary to identify high-risk pregnant women who require oxygen and early hospitalization.

In the present study, we investigated the clinical manifestations, disease severity, and risk factors for developing hypoxemia in pregnant women with SARS-CoV-2 infection.

MATERIALS AND METHODS

Study population and ethics

We performed a retrospective cohort study of pregnant women infected with SARS-CoV-2 who were admitted to the National Health Insurance Service Ilsan Hospital in Goyang or the Wonju Severance Christian Hospital in Wonju, South Korea, between August 2020 and February 2022. COVID-19 was laboratory-confirmed in all women by SARS-CoV-2 real-time RT-PCR. The clinical characteristics and prognoses were compared between pregnant women who required oxygen during their hospitalization and those who did not. The primary outcome of this study was to investigate the risk factors that cause hypoxemic respiratory difficulty in pregnant women infected with SARS-CoV-2. This study was approved by the Institutional Review Board of each hospital (#NHIMC 2021-10-005 and YWMC- CR322069). The requirement for patient consent was waived as this was a retrospective study.

Data collection

The maternal characteristics were obtained from electronic medical records to evaluate risk factors for the development of hypoxemia. Factors such as maternal age at the time of diagnosis of COVID-19, maternal height and weight at admission, gestational age, and body mass index (BMI)—calculated as weight in kilograms divided by the square of the height in meters (kg/m^2)—were assessed. BMI was divided into normal (<25 kg/m^2), obese (25–29.9 kg/m^2), and severely obese (≥30 kg/m^2) at the time of infection using the cut-offs established for the proposed weight classification by BMI in adult Asians.[20] Laboratory parameters such as serum C-reactive protein (CRP) levels, white blood cell count, and cyclic threshold value, including RdRp gene and E gene at admission, were obtained. Information on the immunization status was also collected.

All patients underwent chest radiography at admission. If fever continued, fever occurred, or respiratory symptoms such as coughing or sore throat worsened, a follow-up chest radiography was undertaken additionally to investigate whether additional pneumonia had occurred or worsened. Pneumonia was defined as radiological evidence of abnormalities, such as haziness and consolidation. Considering age ≥35 years at the time of birth is referred to as advanced maternal age, which could be a risk factor for various types of complications, we regarded it as a risk factor, and the pregnancy period at the time of infection was divided into three groups: first trimester (≤14 gestational weeks), second trimester (15–28 gestational weeks), and third trimester (≥29 gestational weeks).

Definitions

Complete vaccination was defined as: 1) the receipt of the second dose in a two-dose vaccine series (BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273 vaccine) at least 2 weeks before study entry or 2) the receipt of a single-dose vaccine (Ad26.COV2.S vaccine) at least 2 weeks before the diagnosis of COVID-19. Partial vaccination was defined as the receipt of at least one dose without meeting the complete vaccination criteria, and booster vaccination was defined as the receipt of a vaccine dose after complete vaccination. The Omicron wave was regarded if an infection occurred after January 2022, as the detection rate of the Omicron variant was 50.3% in the third week of January 2022 in Korea.[21] Of the total of 410 patients, 116 were enrolled during the Omicron wave.

Severity was determined using the WHO ordinal scale for clinical improvement: no oxygen therapy, low flow oxygen by mask or nasal cannula, high flow oxygen or non-invasive ventilation, intubation, mechanical ventilation, ventilation with additional support, and death.[22] All patients were categorized into the oxygen and non-oxygen groups according to the oxy-

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gen requirement for maintaining ≥94% pulse oximetry (SpO_2) during hospitalization. All patients in this study were followed until either symptom recovery or death, even after discharge.

Statistical analysis

Patient data were analyzed and compared. Statistical analyses were performed using Student's t-test for continuous variables, χ^2 test, and Fisher's exact test for categorical variables to compare demographic and clinical characteristics between pregnant in-patients who required oxygen therapy (oxygen group) and those who did not (non-oxygen group). Independent predictors for the development of hypoxemia requiring supplement oxygen were determined by multivariate analysis using a binary logistic regression model. All *p*-values were two-tailed, and a *p*-value <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the study population

During the study period, 410 pregnant women were hospitalized with SARS-CoV-2 infection. The mean age of the patients was 33.3 years, and the median gestational age at SARS-CoV-2 infection diagnosis was 28 weeks (Table 1). Overall, 100 (24.4%) participants required oxygen therapy (oxygen group) and 310 (75.6%) did not require oxygen (non-oxygen group).

Table 1. Demographics and Baseline Characteristics of 410 Pregnant Women Infected with SARS-CoV-2

Characteristics	Total (n=410)	Oxygen requirement (n=100)	No oxygen requirement (n=310)	*p* value
Age (yr)	33.26±4.44	33.56±4.28	33.16±4.49	0.437
IUP (week)	28.04±9.37	30.22±6.99	27.33±9.93	0.001
Symptoms*				
Fever	244 (59.5)	81 (81.0)	163 (52.6)	<0.001
Cough	245 (60.5)	73 (73.0)	172 (56.4)	0.003
Myalgia	142 (35.1)	39 (39.0)	103 (33.8)	0.342
Anosmia	47 (11.6)	13 (13.0)	34 (11.1)	0.616
Diarrhea	4 (1.0)	1 (1.0)	3 (1.0)	>0.999
Presence of pneumonia	160±39.0	84±84.0	76±24.5	<0.001
Body mass index, kg/m^2	25.21±4.80	26.06±5.07	24.93±4.70	0.041
Real-time RT-PCR Ct value at diagnosis				
RdRp gene	19.41±6.21	18.49±5.89	19.72±6.29	0.096
E gene	19.44±5.94	18.76±5.46	19.67±6.08	0.206
CRP, mg/dL	2.27±2.76	4.38±3.84	1.59±1.85	<0.001
Omicron wave	116 (28.3)	18 (18.0)	98 (31.6)	0.009
COVID-19 vaccination status				0.007
Not vaccinated	362 (88.3)	98 (98.0)	264 (85.2)	0.003
Partially	12 (2.9)	1 (1.0)	11 (3.5)	
Completely	34 (8.3)	1 (1.0)	33 (10.6)	
Boosted	2 (0.5)	0 (0.0)	2 (0.6)	
Use of remdesivir	73 (17.8)	70 (70.0)	3 (1.0)	<0.001
Clinical status				
Initial				<0.001
No oxygen	399 (97.3)	89 (89.0)	310 (100)	
Low flow oxygen	10 (2.4)	10 (10.0)	0 (0.0)	
High flow oxygen	1 (0.2)	1 (1.0)	0(0.0)	
Severest during disease progression				<0.001
No oxygen	310 (75.6)	0 (0.0)	310 (100)	
Low flow oxygen	81 (19.7)	81 (81.0)	0 (0.0)	
High flow oxygen	15 (3.7)	15 (15.0)	0 (0.0)	
Mechanical ventilation	4 (1.0)	4 (4.0)	0 (0.0)	
Mortality	0 (0.0)	0 (0.0)	0 (0.0)	

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IUP, intrauterine pregnancy; RT-PCR, reverse transcription polymerase chain reaction; Ct, cyclic threshold; CRP, C-reactive protein; COVID-19, coronavirus disease-2019.
Data are presented as mean±standard deviation, median±standard deviation, or n (%).
*Complained at admission and/or before admission.

In the oxygen group, 70 (70%) patients received remdesivir, whereas in the non-oxygen group, 3 (1.0%) patients received remdesivir (Table 1). Of the 100 patients in the oxygen group, 11 (11%) required oxygen therapy at admission, and the rest required oxygen therapy as the disease course worsened during hospitalization. Most patients (81%) in the oxygen group required only low-flow oxygen throughout their COVID-19 illness. Four patients required mechanical ventilation as the disease progressed. However, no patient died.

Fever and cough were the most common symptoms, and they were more frequent in the oxygen group (81.0% vs. 52.6% and 73.0% vs. 56.4%, respectively). Gestational age (30.22±6.99 vs. 27.33±9.93, p=0.001) and BMI at admission (26.06±5.07 vs. 24.93±4.70, p=0.041) were higher in the oxygen group (Table 1).

COVID-19 immunization status and disease severity

Of the unvaccinated patients, 27.1% (98/362) developed hypoxemia, and approximately 5% required high-flow oxygen or mechanical ventilation. In contrast, only 2 (4.3%) patients needed low-flow oxygen among 46 vaccinated patients (partially, completely, and boosted) (Supplementary Table 1, only online).

Omicron wave and disease severity

Among the total of 410 patients enrolled in the study, 116 patients were enrolled during the Omicron wave. The patients infected during the Omicron wave had a relatively lower frequency of oxygen demand than those infected before the Omicron wave (15.5% vs. 27.9%) (Supplementary Table 2, only online). Considering the late introduction of the vaccine for pregnant women and the late period of Omicron variant dominance, the frequency of oxygen demand as per variant (Omicron vs. other) was compared in the unvaccinated subgroup. A lower frequency of oxygen demand was observed in patients infected during the Omicron wave (19.5% vs. 29.5%), even among unvaccinated patients.

Table 2. Risk Factors for the Development of Hypoxemic SARS-CoV-2 Infection (Multivariate Analysis)

Variables	aOR (95% CI)*	*p* value
Age (≥35 years)	1.386 (0.817–2.351)	0.227
Omicron wave	0.498 (0.258–0.961)	0.038
Trimester period		
First	Ref.	
Second	4.653 (0.977–22.152)	0.053
Third	5.083 (1.095–23.593)	0.038
No vaccination	5.376 (1.193–24.390)	0.028
RdRp gene	0.983 (0.942–1.027)	0.450
CRP (≥1.0 mg/dL) at admission	5.878 (3.099–11.146)	<0.001
BMI at SARS-CoV-2 infection		
<25 kg/m^2	Ref.	
25–29.9 kg/m^2	1.287 (0.742–2.230)	0.369
≥30 kg/m^2	2.247 (0.971–5.197)	0.058

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; aOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; BMI, body mass index.

Risk of hypoxemic respiratory difficulty among SARS-CoV-2-infected pregnant women

In a multivariate logistic regression analysis, the risk of developing hypoxemic respiratory difficulty was significantly associated with SARS-CoV-2 infection during the third trimester [adjusted odds ratio (aOR) 5.083, 95% confidence interval (CI): 1.095–23.593, p=0.038], elevated CRP (≥1.0 mg/dL) at admission (aOR 5.878, 95% CI: 3.099–11.146, p<0.001) and no vaccination (aOR 5.376, 95% CI: 1.193–24.390, p=0.028) (Table 2). However, infection during the Omicron wave (aOR 0.498, 95% CI: 0.258–0.961, p=0.038) was associated with lower odds of developing hypoxemia. The association with severe obesity (BMI ≥30 kg/m^2) was marginally significant (aOR 2.247, 95% CI: 0.971–5.197, p=0.058) (Table 2).

DISCUSSION

The principal finding of this study is that a quarter of women infected with SARS-CoV-2 during pregnancy developed hypoxemic respiratory difficulty and, SARS-CoV-2 infection during the third trimester and no vaccination were independent risk factors for hypoxemic respiratory difficulty.

Previous studies reported that 8%–20% of women infected with SARS-CoV-2 during pregnancy developed hypoxemia.[23-25] Several studies guide SpO_2 to be maintained at 95% or higher to ensure adequate oxygen supply to the fetus. Hypoxemia during pregnancy increases the probability of premature birth, so a disease status of more than moderate severity of COVID-19 can cause adverse effects on pregnant women.

The proportion of patients with oxygen demand was slightly higher in this study than in other studies, and the proportion of patients requiring oxygen therapy at admission was only approximately 10% of the oxygen group.

Pregnant women are somewhat immunosuppressive; therefore, they are particularly susceptible to respiratory pathogens and pneumonia. During pregnancy, physiological adaptive changes such as diaphragm elevation, increased oxygen consumption, and edema of respiratory mucous membrane reduce ventilatory capacity and make them intolerant to hypoxia.[26-28] This study also demonstrated SARS-CoV-2 infection in the third trimester when the diaphragm elevated more and oxygen consumption increased, which could be a risk factor for the development of hypoxemic respiratory difficulty in pregnant women. In addition, hypoxemia is poorly tolerated by the fetus and frequently stimulates preterm labor after mid-pregnancy. Viruses that cause pneumonia, including SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV), have been known to be a threat during pregnancy.[29] Pregnancy is also related to increased disease severity in those infected with

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SARS-CoV-2. A meta-analysis of 92 studies comparing the outcomes between pregnant patients with COVID-19 and age and sex-matched non-pregnant patients with COVID-19 found that pregnancy increases the risk of requiring intensive care, invasive ventilation, and extracorporeal membrane oxygenation.[5] Another meta-analysis of 111 studies found that COVID-19 significantly increases the risk of premature delivery, stillbirth, pre-eclampsia, neonatal mortality, and maternal mortality in pregnant patients infected with SARS-CoV-2 compared to those who are not infected.[30]

Hormonal changes during pregnancy induce immunologic alterations, leading to changes in the severity and susceptibility of infectious diseases during pregnancy.[31] Estradiol is present in high concentrations in pregnant women, and enhances several aspects of innate immunity and both cell-mediated and humoral adaptive immune responses.[32] Progesterone produced by the placenta during pregnancy suppresses the maternal immune responses, including macrophage and natural killer cell activity, and alters the balance between Th1 and Th2 responses.[31,32] As pregnancy advances, T-cell, natural killer cell, and possibly B-cell activities decrease through the complex interplay between sex hormones and the immune system. These changes cause the severity of some infections, such as influenza, to increase in the third trimester of pregnancy.[31,33] Similarly, with COVID-19, studies have reported that the prevalence of symptomatic[34] and severe infections increases in the later stages of pregnancy.[35,36] Previous study in South Korea also revealed that the gestational age of pregnant women was the risk factor for disease severity, especially if infection after 21.5 weeks (late second trimester).[37]

The new Omicron variants appear to be transmitted rapidly, making them more contagious, but the symptoms are milder than those of other variants.[38] Data on the effect of pregnant women with Omicron infection is insufficient; however, even in pregnant women, the Omicron variant is associated with less severe symptoms and high infectivity. Omicron variant cause severe clinical features, including death, among those who did not get vaccinated in the general population.[39] Similarly, Omicron variants can cause adverse maternal and neonatal outcomes, especially in unvaccinated women.

For these reasons, pregnant women are strongly recommended to be vaccinated to reduce the risk of severe COVID-19. Many studies have reported that COVID-19 immunization during pregnancy is safe, effective, and beneficial for both mother and baby. In pregnant women, vaccination is associated with fewer COVID-19 cases during pregnancy.[40,41] Furthermore, pregnant women vaccinated against SARS-CoV-2 have a reduced risk of severe or critical presentation of COVID-19 compared to those not vaccinated.[42]

The Korea Centers for Disease Control and Prevention's recommendation for the use of the COVID-19 vaccine in pregnant women was released only during the latter half of this study, and many pregnant women did not want to be vaccinated despite this recommendation. Although this study was not intended to evaluate the effectiveness of COVID-19 vaccines, given that vaccination was significantly associated with a lower risk of hypoxemic respiratory difficulty, there is a need to encourage pregnant women to vaccinate against COVID-19. Notably, none of the vaccinated pregnant women with COVID-19 in our study required high-flow oxygen or mechanical ventilation.

This study has several strengths. First, we collected complete patient records from two institutions with a uniform protocol for analysis, including epidemiological, laboratory, and radiologic findings, as well as treatment details and clinical outcomes of patients. With these data, multivariate analyses could be performed with correct variables considering the potential confounding factors for severe maternal outcomes, such as BMI or accurate gestational weeks, and all participants were followed up until recovery. Second, all cases were laboratory-confirmed COVID-19 by real-time RT-PCR. We did not include patients with suspected COVID-19 without evidence of a positive PCR result. Lastly, all pregnant women with COVID-19 were hospitalized during the study period, which could provide adequate information about COVID-19 even with mild disease.

This study also has some limitations. First, the Omicron variant infection was not confirmed by sequencing but was designated as the causative strain in the Omicron variant-dominant period. Second, this study included a relatively small number of women from two institutions, which may limit the generalizability of the findings. Further analyses with larger sample sizes are warranted to improve our understanding and strategies for managing COVID-19 in pregnant women.

In conclusion, a quarter of women infected with SARS-CoV-2 during pregnancy developed hypoxemic respiratory difficulty with the requirement of oxygen therapy. SARS-CoV-2-infected pregnant woman increased the risk for the requirement of oxygen during the disease course if she was in the third trimester and did not get vaccinated and the CRP was elevated (≥1.0 mg/dL) at admission.

AUTHOR CONTRIBUTIONS

Conceptualization: Eui Hyeok Kim and Young Keun Kim. Data curation: Yujin Sohn, Jisun Yun, Eui Hyeok Kim, and Young Keun Kim. Formal analysis: Eui Hyeok Kim and Young Keun Kim. Investigation: Hee Kyoung Choi, Eui Hyeok Kim, and Young Keun Kim. Methodology: Eui Hyeok Kim and Young Keun Kim. Project administration: Young Keun Kim. Visualization: Yujin Shon and Young Keun Kim. Writing—original draft: Yujin Sohn and Hee Kyoung Choi. Writing—review & editing: Jisun Yun, Eui Hyeok Kim, and Young Keun Kim. Approval of final manuscript: all authors.

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