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# Clinical Characteristics and Pregnancy-Related Outcomes of Pregnant Women Hospitalized with COVID-19 During the Delta Wave: A Single-Center Observational Study

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## ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) during pregnancy is associated with increased disease severity and an increased risk of perinatal complications. However, few studies of pregnant women with COVID-19 have been conducted in Korea. The purpose of this study was to describe the clinical course and pregnancy outcomes of pregnant women admitted to our hospital with COVID-19 according to the severity.
**Materials and Methods:** This retrospective cohort study included women aged 18 years of age or older who were hospitalized in the Gachon University Gil Medical Center with COVID-19 during pregnancy between July 1, 2021 and January 31, 2022. COVID-19 severity was classified according to the "Criteria for severity classification by symptoms of COVID-19" presented by the Korea Disease Control and Prevention Agency. Severe cases were defined as those who required oxygen treatment administered via a high-flow nasal cannula or invasive mechanical ventilation or should be applied extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy.
**Results:** A total of 103 pregnant women were hospitalized with COVID-19 during the study period. Their mean age was 33 (± 4.14) years, and 4 (3.9%) had been vaccinated against COVID-19. At the time of diagnosis of COVID-19, 3 (2.9%), 33 (32.0%), and 67 (65.1%) patients were in the first, second, and third trimester, respectively. The most common symptoms were cough (99 patients, 96.1%) and fever (85 patients, 82.5%). There was 1 (1.0%) asymptomatic patient. Forty patients (38.8%) required supplemental oxygen and 19 patients (18.4%) had severe disease. Of the 19 severe cases, 7 were in the 2nd trimester and 12 were in the 3rd trimester. Forty-one (39.8%) patients delivered, including two twin deliveries. Of the 41 cases of delivery, 14 were premature, 4 out of 21 (19.0%) in mild, 4 out of 12 (25.0%) in moderate, and 6 out of 8 (75.0%) in severe. Severe disease was associated with an increased rate of preterm birth ($P = 0.012$). Four of the 43 neonates (9.1%) received oxygen treatment.
**Conclusion:** Pregnant women with COVID-19 had a high rate of severe disease and a high preterm delivery rate, especially among those with severe disease.

**Keywords:** COVID-19; SARS-CoV-2; Disease severity; Pregnancy; Premature birth

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## INTRODUCTION

Soon after the discovery of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in December 2019, coronavirus disease 2019 (COVID-19) became pandemic, with the cumulative number of confirmed cases worldwide exceeding 500 million, and over 6 million deaths as of June 2022 [1]. During a prolonged pandemic, the identification of high-risk groups and establishment of priorities for treatment and prevention are important for disease control. Certain comorbidities and medical conditions contribute to the severity of COVID-19 [2], including older age, obesity, malignancy, chronic kidney disease, diabetes, heart disease, lung disease, solid organ transplantation or hematopoietic stem cell transplantation [3], and pregnancy [3-5]. Pregnancy does not increase susceptibility to SARS-CoV-2 infection; however, compared with non-pregnant women of the same age, pregnant women are more likely to experience severe disease, and pregnant women with COVID-19 have an increased risk of preterm delivery and stillbirth [4]. Therefore, the treatment strategy for pregnant women with COVID-19 should consider not only the COVID-19 severity of each patient, but also the well-being of the fetus and an appropriate delivery process. Pregnant women with COVID-19 constitute a patient group that requires more medical resources than other high-risk groups. Moreover, some treatment may be withheld in pregnant women with COVID-19 due to concerns regarding fetal safety, and insufficient prenatal monitoring caused by isolation may adversely affect the prognosis of pregnant women with SARS-CoV-2 infection and their fetuses [6].

Some studies on pregnant women with COVID-19 have been published in the region [7, 8]. However, most published studies have reported on women with mild disease, and there is a paucity of studies on pregnant women with severe COVID-19, and information on risk factors and clinical features that affect the severity is limited. Therefore, it is necessary to study pregnant women with COVID-19 with varying disease severity to identify factors that affect the clinical characteristics, disease severity, and prognosis. Identification of risk factors for severe COVID-19 could facilitate effective triaging and management of patients who require active monitoring and hospitalization.

This study described the clinical course and outcomes of COVID-19 during pregnancy and the perinatal outcome according to the disease severity.

## MATERIALS AND METHODS

### 1. Participants and study center

This single-center retrospective observational study was conducted at Gachon University Gil Medical Center, a tertiary general hospital in Incheon, Korea. The hospital has 1,400 beds, and is designated as a COVID-19 base hospital with 98 beds dedicated to patients with COVID-19, including beds for severe cases. We enrolled pregnant women aged ≥18 years, who were hospitalized in the COVID-19 ward of Gachon University Gil Medical Center between July 1, 2021 and January 31, 2022 and had reverse-transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection on admission.

### 2. Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Gil Medical Center (approval no. GBIRB2021-370). The requirement for written informed consent was

waived because this study used de-identified data that were collected retrospectively. This study adhered to the principles embodied in the Declaration of Helsinki.

### 3. Study Design

We conducted a retrospective cohort study. We used medical records and a pre-admission questionnaire to collect data on age, variant, vaccination history, clinical symptoms, supplemental oxygen demand, chest X-ray and computed tomography (CT) findings, and COVID-19-related medication history (including monoclonal antibody preparations, antiviral drugs, steroids, and immunomodulatory agents). The date of symptom onset was identified from the patient's response in the pre-admission questionnaire. The occurrence of perinatal complications, fetal conditions, delivery outcomes, and birth-related complications was ascertained from post-hospitalization medical records of obstetric and gynecological examinations and delivery records.

### 4. Study measurements and outcomes

The severity of COVID-19 was evaluated according to the Korea Disease Control and Prevention Agency "Criteria for severity classification by symptoms of COVID-19" and the participants were divided into 3 categories comprising a total of 8 subcategories as follows: mild cases, including (1) asymptomatic or (2) symptomatic patients who did not require supplemental oxygen treatment; moderate cases, with oxygen saturation less than 95% who received oxygen treatment administered via (3) a nasal cannula or (4) oxygen mask; and severe cases, including those who required oxygen treatment administered via (5) a high-flow nasal cannula, (6) invasive mechanical ventilation, or (7) extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy, and (8) patients who died [9].

Gestational status was defined as the first trimester from the date that the pregnancy was confirmed to 13 weeks and 6 days; the second trimester extended from 14 weeks and 0 days to 27 weeks and 6 days; and the third trimester extended from 28 weeks and 0 days until delivery. With regard to the perinatal outcome, gestational age above 37 weeks and 0 days and less than or equal to 36 weeks and 6 days was used to classify a term delivery and a preterm birth, respectively.

### 5. Statistical analysis

Results were expressed as the mean ± standard deviation (SD) or frequency and percentage. Continuous variables were compared between groups using independent samples *t*-tests. Categorical variables were compared between groups using Chi-square tests or Fisher's exact test. All tests were two-tailed, and *P* values <0.05 were considered statistically significant. Risk factors were reported as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed using IBM SPSS version 26.0 for Windows (IBM Corp., Armonk, NY, USA).

## RESULTS

During the study period, a total of 103 pregnant women with confirmed COVID-19 were admitted to Gachon University Gil Medical Center. The distribution of the number of patients by the time of diagnosis is described in **Table 1**. **Supplementary Figure 1** shows the number of weekly confirmed cases nationwide and the distribution of patients enrolled in the study during the study period.


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**Table 1.** Demographic characteristics and medical history of the participants

| Characteristic | Value (n = 103) |
|---|---|
| Age, mean (SD), years | 33 (± 4.14) |
| Age group, years | |
| ≤24 | 2 (1.9%) |
| 25 - 29 | 11 (10.7%) |
| 30 - 34 | 50 (48.5%) |
| 35 - 39 | 33 (32.0%) |
| ≥40 | 7 (6.8%) |
| Nationality | |
| Korean | 91 (88.3%)[a] |
| Non-Korean | 12 (11.7%)[b] |
| Comorbidities | |
| None | 86 (83.5%) |
| Hyperthyroidism | 4 (3.9%) |
| Hypothyroidism | 5 (4.9%) |
| Preexisting diabetes mellitus | 3 (2.9%) |
| Asthma | 3 (2.9%) |
| Others | 5 (4.9%)[c] |
| COVID-19 vaccination | |
| None | 99 (96.1%) |
| 2 doses | 4 (3.9%)[d] |
| Variant | |
| Unknown | 85 (82.5%) |
| B.1.617 (Delta) | 18 (17.5%) |
| Time of diagnosis | |
| July 1 to August 31, 2021 | 15 (14.6%) |
| September 1 to October 31, 2021 | 27 (26.2%) |
| November 1 to November 30, 2021 | 25 (24.3%) |
| December 1[e] to December 31, 2021 | 27 (26.2%) |
| January 1 to January 31, 2022 | 9 (8.7%) |
| Gestational age at COVID-19 diagnosis | |
| First trimester (13 + 6/7 weeks) | 3 (2.9%) |
| Second trimester (14 + 0/7 to 27 + 6/7 weeks) | 33 (32.0%) |
| Third trimester (28 + 0/7 to 40 + 6/7 weeks) | 67 (65.1%) |
| Gravidity | |
| Primigravida | 53 (51.5%) |
| Multigravida | 50 (48.5%) |
| Number of fetuses | |
| Singleton | 98 (95.1%) |
| Multiple (twin) | 5 (4.9%) |

[a]Includes 2 naturalized citizens from Vietnam.
[b]Includes 1 Kazakh, 2 Uzbek, 2 Vietnamese, 4 Chinese, 1 Indonesian, 1 American, and 1 Thai citizen(s).
[c]Multiple choices are possible; includes 1 patient each with pulmonary tuberculosis, carotid arterial stenosis, allergic rhinitis, anxiety disorder, and chronic hepatitis B virus infection.
[d]Includes 3 patients who had received 2 doses of the BNT162b2 (Pfizer-BioNTech, New York, NY, USA) vaccine and 1 patient who had received 2 doses of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca, Andong, Korea) vaccine.
[e]On December 1, 2021, the first Omicron variant of COVID-19 was confirmed in Korea.
SD, standard deviation; COVID-19, coronavirus disease 2019.

## 1. Participant demographic characteristics and medical history

The participant demographic characteristics and medical history are shown in **Table 1**. At the time of diagnosis, the average age of the patients was 33 (± 4.14) years (range: 21 - 44 years). Of the patients, 91 were Korean and 12 were non-Korean. All of the patients were Asian and living in Korea. Comorbidities included hyperthyroidism (n = 4), hypothyroidism (n = 5), asthma (n = 3), and diabetes mellitus (n = 3). Only 4 patients (3.9%) had been vaccinated against COVID-19: 2 patients had received 2 doses prior to becoming pregnant; 1 received the first dose prior to becoming pregnant and the second dose during pregnancy; and 1 received the first dose during pregnancy. The remaining 99 patients (96.1%) were unvaccinated


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against COVID-19. The B.1.617 (Delta) variant was detected in 18 patients, and the variant status of the remaining 85 patients was unknown. The patients included 53 (51.5%) primigravida and 50 (48.5%) multigravida women, of whom 98 (95.1%) had singleton pregnancies and 5 (4.9%) had twin pregnancies. At the time of diagnosis of COVID-19, 3 (2.9%), 33 (32.0%), and 67 (65.1%) patients were in the first, second, and third trimester, respectively (**Fig. 1**).

## 2. Clinical characteristics

The participant clinical characteristics are shown in **Table 2**. The average duration from symptom onset to diagnosis and hospitalization was 1.3 and 3.4 days, respectively. The most common symptoms were cough (99 patients, 96.1%) and fever (85 patients, 82.5%), whereas 37 patients (35.9%) experienced dyspnea.

Sixty-three patients (61.2%) did not require oxygen treatment throughout their hospital stay; 21 patients (20.4%) received oxygen via a nasal cannula; 17 patients (16.5%) received oxygen via a high-flow nasal cannula; 1 patient (1.0%) was treated with invasive mechanical ventilation, and another patient (1.0%) received invasive mechanical ventilation, ECMO, and continuous renal replacement therapy. All 40 patients who received oxygen treatment were unvaccinated. Seven patients (6.8%) required supplemental oxygen administration from the time of hospital admission. The other 33 patients (32.0%) who received oxygen treatment did not need oxygen supplementation at the time of hospital admission, but required it later during the clinical course of the disease. Among the patients who received oxygen, the average period from symptom onset to initiation of oxygen administration was 6.6 (± 2.8) days, and the average duration of oxygen administration was 6.5 (± 5.1) days.

In the participant cohort, 34 patients (33.0%) had confirmed pneumonia on anterior-posterior chest X-ray performed on admission, of which 8 patients (7.8%) had unilateral lesions and 26 patients (25.2%) had bilateral lesions. Among the 69 patients (67.0%) with a normal chest X-ray on admission, 30 patients (29.1%) newly developed lung lesions, among whom 6 (5.8%) developed unilateral lesions and 24 (23.3%) developed bilateral lesions. One patient (1.0%) refused X-ray imaging.

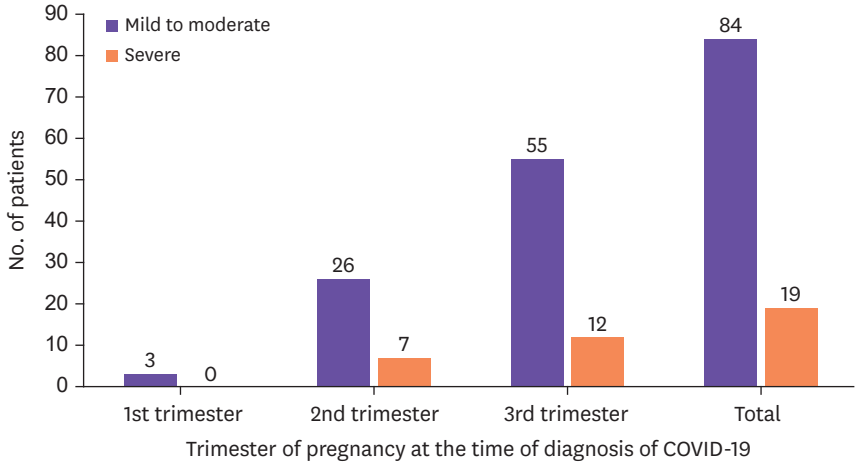


**Figure 1.** Severity of COVID-19 according to gestational age at the time of diagnosis of COVID-19.
COVID-19, coronavirus disease.


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**Table 2.** Clinical characteristics of the participants

| Characteristic | Value (n = 103) |
|---|---|
| Symptoms[a] | |
| Fever | 85 (82.5%) |
| Chills | 20 (19.4%) |
| Myalgia | 40 (38.8%) |
| Headache | 29 (28.2%) |
| Rhinorrhea/nasal congestion | 59 (57.3%) |
| Sore throat | 58 (56.3%) |
| Anosmia/ageusia | 13 (12.6%) |
| Cough | 99 (96.1%) |
| Sputum | 65 (63.1%) |
| Dyspnea | 37 (35.9%) |
| Nausea/vomiting | 3 (2.9%) |
| Diarrhea | 3 (2.9%) |
| Asymptomatic | 1 (1.0%) |
| Maximal oxygen demand | |
| Room air | 63 (61.2%) |
| Low flow | 21 (20.4%) |
| High flow | 17 (16.5%) |
| Invasive mechanical ventilation | 1 (1.0%) |
| ECMO | 1 (1.0%) |
| Abnormal radiologic findings | |
| None | 39 (37.9%) |
| Pneumonic infiltration | 64 (62.1%) |
| On admission | 34 (33.0%) |
| Follow-up during hospitalization | 30 (29.1%) |
| Treatment[a] | |
| Glucocorticoid | 65 (63.1%) |
| Remdesivir | 26 (25.2%) |
| Regdanvimab | 10 (9.7%) |
| Tocilizumab | 2 (1.9%) |

[a]Multiple items may be listed for each participant.
ECMO, extracorporeal membrane oxygenation.

## 3. Treatment

Participant treatment is shown in **Table 2**. Thirty-four patients (33.0%) were monitored and treated symptomatically. The most frequently used medication was glucocorticoids, which was administered to 65 patients (63.1%; 26 mild, 20 moderate, and 19 severe cases). Remdesivir (Gilead Sciences, Inc., Foster city, CA, USA) was administered to 26 (25.2%) patients (8 moderate and 18 severe cases). Glucocorticoids were administered to all participants who used remdesivir. Regdanvimab (CELLTRION INC., Incheon, Korea), a passive antibody treatment, was administered to 10 patients (9.7%; 3 mild and 7 moderate cases), all of whom initiated the medication postpartum. Tocilizumab (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was administered postpartum to two patients (1.9%) who required mechanical ventilation.

## 4. Patient outcomes

The average length of hospital stay of the patients was 11.5 (± 4.50) days. Of the participant cohort, 102 patients (99.0%) improved and were discharged without specific sequelae, and 1 patient (1.0%) died of septic shock during ECMO treatment. The most common obstetric complication was preterm labor, which was confirmed in 9 patients (8.7%). Gestational diabetes was identified in 5 patients (4.9%), premature membrane rupture in 4 patients (3.9%), and placenta previa in 2 patients (1.9%). Eighteen patients (17.5%) were diagnosed with bacterial vaginosis or candidiasis and were treated accordingly.


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Forty-one (39.8%) patients were confirmed to have delivered, of whom 37 (35.9%) delivered during treatment in isolation (**Table 3**). Four patients delivered after being released from quarantine. Forty patients delivered by cesarean section and one patient had a vaginal delivery after being released from quarantine. Of the 41 patients on whom we had delivery information, 27 (65.9%) delivered at term (after 37 weeks), and 14 (34.1%) delivered preterm (before 37 weeks). Among the preterm births, there were 5 neonates were early preterm births of before 34 weeks gestation. Of the 41 patients on whom we had delivery information, 8 (19.5%) had severe disease, of whom 2 delivered at term and 6 delivered preterm. Of the 40 patients with moderate or severe disease, 10 had a preterm birth before 37 weeks, accounting for 71.4% of the 14 preterm births (**Fig. 2**). Of the 19 patients with severe disease, 8 (42.1%) gave birth, of whom 6 (31.6%) were premature. Of the 63 patients with mild disease, 21 (33.3%) gave birth, and 4 (6.3%) had a preterm birth. In addition to preterm births, the proportion of early term births at 37 to 38 weeks of age was also increased (**Supplementary Table 1**).

The reasons for preterm delivery were maternal COVID-19 worsening in 5 patients, premature labor in 7 patients, and fetal conditions other than premature labor in 2 patients. Both patients who delivered preterm due to fetal conditions other than preterm labor had twin pregnancies, of whom 1 patient had a decreased cervical length due to fetal descent, and the other patient had an intrauterine fetal death due to twin-to-twin transfusion syndrome (TTTS).

Among the patients who delivered during isolation, 4 experienced postpartum complications, including uterine atony, intrauterine hematoma, postdural puncture headache, and septic shock caused by multidrug-resistant *Acinetobacter baumannii*.

**Table 3.** Gestational age at delivery according to severity of COVID-19

| Gestational age at delivery | Disease severity | | All (n = 41) | OR[a] (95% CI) |
|---|---|---|---|---|
| | Mild to moderate (n = 33) | Severe (n = 8) | | |
| Term (≥37 weeks) | 25 (76.0%) | 2 (25.0%) | 27 (65.9%) | 1.0 (reference) |
| Preterm (<37 weeks) | 8 (24.0%) | 6 (75.0%) | 14 (34.1%) | 9.38 (1.57 – 56.01) |

[a]*P* = 0.012 for the overall outcome.
COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval.

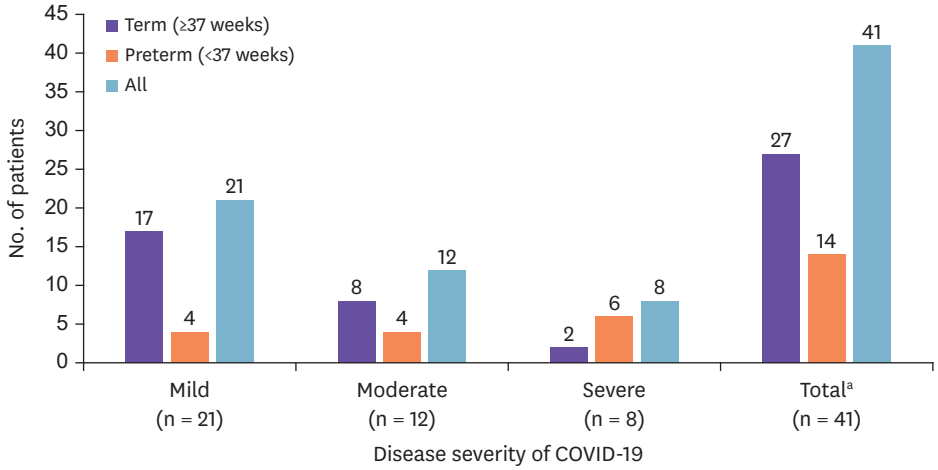


**Figure 2.** Perinatal outcomes according to COVID-19 severity.
[a]Among the 41 patients with confirmed delivery, 1 was in the second trimester, and 40 were in the third trimester at the time of diagnosis of COVID-19. The patient who was confirmed with COVID-19 in the second trimester of pregnancy was mild, and it was confirmed that they had a full-term delivery after release from quarantine.
COVID-19, coronavirus disease 2019.


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### 5. Neonatal outcome

There were a total of 43 births, including two pairs of twins. Four of the 43 neonates required oxygen therapy (1 via nasal tip, 2 via continuous positive airway pressure, and 1 via ventilator). Five neonates had atrial septal defects confirmed by ultrasonography shortly after delivery. One intrauterine fetal death and one neonatal death occurred in a pair of twins with TTTS.

## DISCUSSION

This study was conducted among 103 women hospitalized with COVID-19 in a single hospital during pregnancy, of whom 65.1% were in the third trimester of pregnancy. Until November 25, 2021 in Korea, all pregnant women who were confirmed with COVID-19 were hospitalized. From November 26, 2021, the policy has been changed to only provide inpatient treatment for pregnant women with symptoms such as abdominal pain, labor pain and vaginal bleeding. In this study, 62 patients were hospitalized during the former period, and 26 deliveries were confirmed. Forty-one patients were hospitalized during the latter period and 15 deliveries were confirmed.

The main clinical symptoms were cough and fever, followed by sputum, rhinorrhea, and sore throat, and more than one third of the participants complained of myalgia and dyspnea. Only one patient was asymptomatic. Previous studies [5, 10] comparing the clinical course of pregnant women with confirmed COVID-19 with that of non-pregnant women with COVID-19 found that cough and fever were the most common symptoms in both groups. However, in previous studies of pregnant women with COVID-19, the participants had fewer symptoms, such as cough, sore throat, and headache in addition to fever, and a larger proportion of the patients had mild or asymptomatic course. In the present study, there were few asymptomatic patients because the patients were admitted to hospital either because they were symptomatic or because they were in the second half of pregnancy with a high probability of delivery, as ascertained through the pre-admission questionnaire and bed allocation procedure.

The comorbidities in order of decreasing frequency were hypothyroidism, hyperthyroidism, diabetes mellitus, and asthma. Three patients had preexisting diabetes and 5 patients had gestational diabetes, which constitutes a high-risk group for severe COVID-19 [3]. A meta-analysis of studies of pregnant women with SARS-CoV-2 infection [5] found that preexisting diabetes was a risk factor for severe disease, intensive care unit (ICU) admission, invasive ventilation, and maternal death. Gestational diabetes has been found to increase severe disease, ICU admission, and preterm birth [11]. This study did not find any statistically significant results regarding an association between diabetes and disease severity and complications due to the limited number of patients with diabetes or gestational diabetes.

In this study, 40 patients (38.8%) had moderate to severe disease, and 19 patients (18.4%) had severe disease, and 1 death (1.0%). In a domestic study[7] based on data from the Health Insurance Review and Assessment Service, the mortality rate among non-pregnant women aged 20 to 44 years with COVID-19 was 0.04%, and 1.7% had moderate to severe disease. The other study found that the rate requiring oxygen treatment with nasal cannula was 6.4% among the 78 pregnant women with COVID-19 from January 2020 to February 2021 and there no cases of severe disease or death. However, in this study that included a large number of pregnant women with more than moderate severity, 20.4% of patients received oxygen treatment via a nasal cannula, indicating that the patients in our study had more


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severe disease. In this study, all of the patients were infected after July 2021 following the emergence of the Delta variant. As the Delta variant became the dominant strain, the average daily number of confirmed cases in Korea exceeded 1,000 during this period, and the number of moderate and severe cases increased [12]. As the Delta variant tends to cause more severe disease, this explains the relatively high proportion of patients with severe disease in this study. Adhikari et al. [13] showed similar results in a study that analyzed the change in the number and severity of COVID-19 pregnant patients in a single institution in the United States until September 2021 after the Delta variant emerged. There were 6,755 COVID-19 deaths in Korea during the study period, of which 155 deaths (2.3%) were in individuals aged 20 to 49 years, a case fatality rate of 0.1% [14]. Since there is only 1 death in this study, it is difficult to compare the mortality with national mortality statistics directly. Nevertheless, it is meaningful as the first case of death of a pregnant woman with COVID-19 in Korea. It shows that the severity is higher than those of non-pregnant patients of the same age group. This is consistent with the results shown in studies conducted in other countries, which have shown that pregnant women are more likely to be admitted to the ICU and to require invasive ventilator intubation and ECMO treatment, and have a higher risk of progression to severe disease and a higher mortality rate than non-pregnant women [4, 5].

According to Korean birth statistics [15, 16], the proportion of infants born before 37 weeks gestation was 8.1% in 2019 and 8.5% in 2020. The rate of preterm birth in this study was 34.1%, which is more than four times higher than the national birth statistics. It was also confirmed that women with more severe disease had a significantly higher risk of preterm birth. Early term infants are also known to have significant differences in long-term complications and mortality compared to full term infants born at over 39 weeks' gestation [17]. Since our hospital is designated as a COVID-19 dedicated hospital and high-risk maternity center, pregnant patients admitted to our hospital may have a higher than average risk of preterm birth, so there may have been some selection bias. Nevertheless, it is noteworthy that the frequency of preterm births increased according to the disease severity, and the increased proportion of early preterm births is particularly noteworthy. Recently, Metz et al. [18] who investigated the relationship between maternal and neonatal outcome and SARS-CoV-2 infection due to perinatal complications identified that the risk of neonatal death, preterm birth at less than 37 weeks' gestation, and preterm birth at less than 32 weeks' gestation were higher in women with moderate or severe COVID-19 than in pregnant women without COVID-19, but the investigators did not find a significant difference between women with mild or asymptomatic disease and uninfected women. Prochaska et al. [19] found a significantly increased incidence of maternal vascular malperfusion in the placenta in pregnant women with COVID-19, which could affect the increase in fetal loss or preterm birth. In addition, the study showed that hypercoagulability and placental inflammatory reaction found in the placenta of pregnant women with COVID-19 can induce an inflammatory response in the fetus and negatively affect several systems, including the nervous system, even in the absence of SARS-CoV-2 infection in the infant. Therefore, monitoring of short- and long-term complications of infants born to women with COVID-19 is necessary.

Difficulty in appropriate obstetric treatment due to isolation of pregnant women with COVID-19 may affect neonatal outcomes. In the case of the patient in this study who gave preterm birth due to TTTS, the patient was admitted to an isolation unit as she was not admitted to the Maternal and Fetal Intensive Care Unit due to COVID-19, despite the need for close monitoring with hospitalization. Although the patient has recovered from moderate COVID-19 requiring oxygen, she lost her babies due to intrauterine fetal and neonatal death.

This case shows the need for a dedicated medical institution that can provide both facilities for maternal and fetal monitoring, as well as isolation.

While conducting this study, there were four major types of therapeutic agents available in Korea: steroids, including dexamethasone; the monoclonal antibody agent, regdanvimab; the antiviral drug, remdesivir; the interleukin-6 inhibitor, tocilizumab; and the Janus kinase inhibitor, baricitinib. Steroids can be effectively used in pregnant women who require oxygen administration or fetal lung maturation due to preterm birth [4, 20]. There were no data for regdanvimab on the outcome of administration in pregnant and lactating women [21]. Therefore, it was administered only to women who had given birth and were not lactating, and 7 out of 10 patients who received it were also treated with steroids or remdesivir due to an increased oxygen demand. The safety of remdesivir for pregnant women and the fetus has been confirmed in several studies, and if necessary, it is recommended not to withhold administration [22, 23]. The American College of Rheumatology and National Institutes of Health do not recommend tocilizumab for pregnant women due to safety concerns, and safety information on baricitinib is also insufficient [24]. As such, there were very limited treatment options available to the study participants, compared to non-pregnant patients with COVID-19. In particular, the lack of a treatment with proven safety and effectiveness for pregnant women with mild or less severe disease, and the lack of treatment options other than remdesivir and steroids in pregnant women with moderate or severe disease serve as major factors contributing to the increase severity of the disease in pregnant women.

In the case of Nirmatrelvir/ritonavir (Paxlovid®, Pfizer Inc., New York, NY, USA) that is currently available, its component, ritonavir, has a history of extensive use in pregnant women with Human Immunodeficiency Virus infection [25, 26]. In addition, while nirmatrelvir is thought to be usable for pregnant women based on its mechanism of action and preclinical data, its safety in pregnant women with COVID-19 needs further confirmation. Molnupiravir (Merck & Co., Inc., Rahway, NJ, USA) has been confirmed to be toxic in animal studies and is not recommended for use in pregnant women [20]. At the time of this study, oral administration of drugs was not available because they had not yet been introduced in Korea. There is a need for follow-up studies on the safety and preventive effects on progression to severe when administrating Nirmatrelvir/ritonavir (Paxlovid®, Pfizer Inc., USA).

The role of vaccination in pregnant women is more critical than in other risk groups as the treatment options for their COVID-19 are limited. All four vaccinated patients in this study had mild disease, showing no obstetric complications until discharge. Only one in four had bilateral pneumonia but recovered without oxygen treatment. Although the number of the vaccinated women included in the study was too small for the result to be statistically significant, it is encouraging that none of the vaccinated patients progressed to severe disease.

Although vaccination against COVID-19 in Korea started in February 2021, the vaccination recommendation for pregnant women was not announced until September 27, 2021 [27]. Accordingly, vaccination of pregnant women only became available from October 18, 2021 [28]. From January to December 2021, there were a total of 431,441 pregnant women with COVID-19 vaccine, of whom 389,477 (90.2%) were unvaccinated. A total of 41,964 pregnant women were vaccinated against COVID-19 only once (1st dose: 5,485, 2nd dose: 29,343, and booster dose: 7,136), accounting for less than 10% of pregnant women with COVID-19. During the same period, the number of fully vaccinated pregnant women aged 18 to 49 years in the United States exceeded 60.0% [29]. COVID-19 vaccination in known to lower the risk of infection in pregnant


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women and is not associated with complications of pregnancy or childbirth [30, 31]. However vaccination rates have remained low due to anxiety about the vaccine, negative information, and a lack of awareness of the risk of severe COVID-19. Therefore, medical staff' need to recommend and promote vaccination in order to increase the vaccination rate.

This study has an advantage that it showed a changed pattern from that in the early stage of pandemic, including a large number of pregnant patients during the epidemic wave caused by the Delta variant. This study had a relatively large sample size and a high proportion of severe cases compared to previous studies on COVID-19 in pregnant women in South Korea. As this study was conducted at a single medical institution, most of patients were from in the metropolitan area such as Seoul, Gyeonggi, and Incheon due to the location of the institution. However, patients in the metropolitan area accounted for 70.0% among the cumulative confirmed cases of COVID-19 in Korea during the study period [13].

This study has some limitations. First, there was no control group of non-pregnant women with COVID-19 to use as a basis for comparison. Second, COVID-19 vaccination coverage was too low determine whether vaccination reduced disease severity. Third, in evaluating the relationship between COVID-19 and premature birth, it was difficult to ascertain the effect of other factors, such as diabetes mellitus, and other underlying diseases. Forth, the study did not include women infected with the Omicron variant, which was determined to be predominant at the end of the research. As the clinical features of COVID-19 due to the Omicron variant differ from those of the wild type virus and the Delta variant, further studies are required to determine the clinical characteristics and pregnancy outcomes of pregnant women infected with the SARS-CoV-2 Omicron variant.

In conclusion, pregnant women with confirmed COVID-19 had higher progression rates to severe conditions compared to non-pregnant women of a similar age with COVID-19, and higher preterm birth rates compared to pregnant women without COVID-19. Although pregnant women have many restrictions with regard to availability of treatment for COVID-19, they still have a low vaccination rate. Therefore, it is necessary to make an effort to increase the vaccination rate in order to prevent the pregnant women with COVID-19 progressing to severe disease.

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## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Perinatal outcomes according to COVID-19 severity

**Click here to view**

### Supplementary Figure 1

Number of weekly confirmed cases in Korea and number of pregnant patients included in the study by week.

**Click here to view**

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