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Maternal Outcomes and Clinical Characteristics of COVID-19 in Korean Pregnant Women during the Early Period of the Pandemic

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ABSTRACT

The present study aimed to compare the clinical characteristics and outcomes between pregnant women and non-pregnant women of childbearing age (20–49 years old) diagnosed with coronavirus disease 2019 (COVID-19) during the initial stage of the COVID-19 pandemic in the Republic of Korea. This nationwide observational study included the information of COVID-19 patients collected by the Korea Disease Control and Prevention Agency from January 2020 to April 2021. Among 5,647 COVID-19 patients, 2,444 (43.3%) were women of childbearing age and 19 were pregnant. None of the pregnant women died. However, 4 deaths occurred among non-pregnant women aged 20–49 years. None of the 19 pregnant women with COVID-19 were admitted to the intensive care unit: they were admitted to the general ward, and none of them required supplemental oxygen. In conclusion, none of the pregnant women with COVID-19 experienced severe infection or death, unlike non-pregnant women of childbearing age.

Keywords: COVID-19; SARS-CoV-2; Pregnancy

The ongoing coronavirus disease 2019 (COVID-19) pandemic is one of the most significant public health threats in modern history and has changed many aspects of medical care and the daily lives of various people. Until recently, many of the response strategies against this pandemic have been based on previous experience with other highly pathogenic coronaviruses such as severe acute respiratory syndrome and Middle East respiratory syndrome.[1,2] As the virologic, epidemiologic, and clinical aspects of this emerging infectious disease are gradually revealed, the effects of severe acute respiratory syndrome coronavirus-2 on a possibly vulnerable subpopulation are currently investigated. The anatomic, physiologic, and immunologic changes that occur as a normal part of pregnancy may cause pregnant women to be more susceptible and vulnerable to viral infections.[3]

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the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

All authors have no potential conflicts of interest to declare.

Author Contributions

Conceptualization: Yoon YK. Data curation: Choi DH. Formal analysis: Choi DH. Funding acquisition: Yoon YK. Project administration: Yoon YK. Software: Choi DH. Supervision: Ilagen JG, Lee J, Yoon YK. Validation: Chung Y, Yoon YK. Visualization: Chung Y. Writing - original draft: Chung Y. Writing - review & editing: Yoon YK.

However, the susceptibility of pregnant women to COVID-19 and related complications remains controversial and unresolved. Data on the clinical impact of COVID-19 on pregnant women in the Republic of Korea (ROK) are limited.[4-8] This information is critical to assessing the risk-benefit of a COVID-19 vaccine, whose Food and Drug Administration approval for use among pregnant women is still pending. Therefore, this study aimed to investigate the clinical characteristics and outcomes in pregnant women diagnosed with COVID-19 during the early stage of the COVID-19 pandemic.

This observational multicenter cohort study was performed using a nationwide database obtained from the medical records from multiple Korean hospitals. In collaboration with Korea Disease Control and Prevention Agency (KDCA) and the National Medical Center, the demographic, epidemiological, and early clinical information of confirmed COVID-19 patients were collected from the government registry from January 2020 to April 2021. After extracting the relevant information from the KDCA database, we compared the maternal outcomes and clinical characteristics of pregnant women diagnosed with COVID-19 with those of non-pregnant women of childbearing age at the onset of the pandemic in Korea. All patients underwent reverse-transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis of COVID-19.

Data on age, sex, body mass index (BMI), clinical symptoms at the time of diagnosis (pharyngitis, runny nose, myalgia, fatigue, dyspnea, headache, change of consciousness, nausea, and diarrhea), intensive care unit (ICU) admission, supplemental oxygen requirement, mechanical ventilation, multiple organ failure, death, comorbidities (diabetes, hypertension, chronic heart disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cancer, chronic liver disease, autoimmune disease, and dementia), and complete blood count (CBC) were obtained. Statistical tests including χ^2 test, Fisher's exact test, Mantel-Haenszel test, and Mann-Whitney U test were used according to the characteristics of the data.

From January 2020 to April 2021, 5,647 COVID-19 patients were included in the registry. Among these patients, 3,327 (58.9%) were women, and 2,444 were women of childbearing age. A total of 19 patients were pregnant women: 5 (26.3%) were aged 20–29 years; 13 (68.4%) were aged 30–39 years, and 1 (5.3%) was aged 40–49 years.

The mortality rates among the total study patients and female patients were 4.3% and 3.5%, respectively. No deaths occurred among pregnant women, while four (0.16%) deaths occurred among women of childbearing age. The median period (interquartile range, IQR) from COVID-19 diagnosis to death in women of childbearing age was 23 (11–37) days. In all patients, the duration between diagnosis of COVID-19 and release from isolation was 23 (18–31) days or 24 (18–32) days for women of childbearing age, and 22 (18–38) days for pregnant women.

All pregnant women in the case group were admitted to the general ward, whereas 21 patients in the control group (0.87%) were admitted to the ICU ($P = 1.000$). None of the pregnant women required supplemental oxygen, while 70 non-pregnant women of childbearing age required supplemental oxygen with or without mechanical ventilation.

None of the pregnant women had comorbidities, while the control group had various pre-existing conditions (**Table 1**). No significant difference was found in the clinical symptoms between the two groups (**Table 1**). Six of the 19 pregnant women were asymptomatic.

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Table 1. Overview of the demographic and clinical characteristics of patients with COVID-19

Demographic characteristics	Total male and female patients, non-pregnant (n = 5,628)	Total non-pregnant women (n = 3,308)	Non-pregnant women aged 20 to 49 years (n = 2,425)	Pregnant women (n = 19)	*P* value[a]	*P* value[b]	*P* value[c]
Age, yr					< 0.001[d]	< 0.001[d]	< 0.001[d]
20–29	1,119 (46.14)	569 (41.72)	1,119 (46.14)	5 (26.32)			
30–39	564 (23.26)	295 (21.63)	564 (23.26)	13 (68.42)			
40–49	742 (30.6)	500 (36.66)	742 (30.6)	1 (5.26)			
BMI, kg/m^2					0.729[e]	0.831[e]	0.919[e]
< 18.5	260 (4.62)	173 (5.23)	106 (4.37)	1 (5.26)			
18.5–22.9	1,867 (33.17)	1,253 (37.88)	923 (38.06)	8 (42.11)			
23.0–24.9	1,039 (18.46)	552 (16.69)	410 (16.91)	2 (10.53)			
25.0–29.9	1,052 (18.69)	476 (14.39)	461 (19.01)	3 (15.79)			
≥ 30	208 (3.7)	109 (3.3)	132 (5.44)	1 (5.26)			
Comorbidities							
Diabetes mellitus	691 (12.28)	366 (11.06)	69 (2.85)	0 (0.00)	0.157[e]	0.258[e]	1.000[e]
Hypertension	1,201 (21.34)	695 (21.01)	118 (4.87)	0 (0.00)	0.021[e]	0.020[e]	1.000[e]
Heart failure	59 (1.05)	37 (1.12)	2 (0.08)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Cardiovascular diseases	179 (3.18)	92 (2.78)	17 (0.7)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Asthma	128 (2.27)	82 (2.48)	46 (1.9)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Chronic obstructive pulmonary disease	40 (0.71)	15 (0.45)	2 (0.08)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Chronic kidney disease	55 (0.98)	29 (0.88)	7 (0.29)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Malignancy	145 (2.58)	96 (2.9)	28 (1.15)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Chronic liver disease	83 (1.47)	35 (1.06)	25 (1.03)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Autoimmune disease	38 (0.68)	26 (0.79)	6 (0.25)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Dementia	224 (3.98)	153 (4.63)	1 (0.04)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Mortality							
Yes	241 (4.28)	114 (3.45)	4 (0.16)	0 (0.00)	-	-	-
Time between diagnosis of COVID-19 and death, median days, IQR	11 (6, 20)	10 (6, 19)	23 (10.5, 37)	-			
No	5,387 (95.72)	3,194 (96.55)	2,421 (99.84)	19 (100.00)	0.836[f]	0.852[f]	0.541[f]
Time between diagnosis of COVID-19 and release from isolation, median days, IQR	24 (18, 32)	24 (18, 32)	23 (18, 31)	22 (18, 38)			
Admission					1.000[e]	1.000[e]	1.000[e]
Intensive care unit	189 (3.36)	74 (2.24)	21 (0.87)	0 (0.00)			
General ward	5,410 (96.13)	3,216 (97.22)	2,404 (99.13)	19 (100)			
Clinical severity of COVID-19					0.596[e]	0.564[e]	0.793[e]
No oxygen therapy	4,455 (79.16)	2,648 (80.05)	2,198 (90.64)	19 (100)			
Nasal cannula	469 (8.33)	268 (8.1)	60 (2.47)	0 (0.00)			
Oxygen mask	43 (0.76)	20 (0.6)	5 (0.21)	0 (0.00)			
Non-invasive ventilation	33 (0.59)	16 (0.48)	4 (0.16)	0 (0.00)			
Invasive ventilation	19 (0.34)	9 (0.27)	1 (0.04)	0 (0.00)			
Multi-organ failure or ECMO	11 (0.2)	4 (0.12)	0 (0.00)	0 (0.00)			
Symptoms							
Fever	1,305 (23.19)	784 (23.7)	512 (21.11)	3 (15.79)	0.591[e]	0.590[e]	0.780[d]
Cough	2,341 (41.6)	1,423 (43.02)	990 (40.82)	6 (31.58)	0.374[e]	0.312[e]	0.408[e]
Sputum	1,619 (28.77)	1,027 (31.05)	659 (27.18)	6 (31.58)	0.788[e]	0.961[e]	0.667[e]
Pharyngitis	881 (15.65)	591 (17.87)	449 (18.52)	2 (10.53)	0.756[e]	0.556[e]	0.555[e]
Rhinorrhea	621 (11.03)	382 (11.55)	327 (13.48)	3 (15.79)	0.459[e]	0.475[e]	0.735[e]
Myalgia	926 (16.45)	600 (18.14)	387 (15.96)	4 (21.05)	0.539[e]	0.764[e]	0.529[e]
Fatigue	234 (4.16)	134 (4.05)	83 (3.42)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Dyspnea	666 (11.83)	403 (12.18)	164 (6.76)	0 (0.00)	0.156[e]	0.156[e]	0.635[e]
Headache	967 (17.18)	668 (20.19)	454 (18.72)	2 (10.53)	0.759[e]	0.398[e]	0.555[e]
Altered mental status	35 (0.62)	19 (0.57)	2 (0.08)	0 (0.00)	1.000[e]	1.000[e]	1.000[e]
Nausea or vomiting	244 (4.34)	176 (5.32)	83 (3.42)	1 (5.26)	0.570[e]	1.000[e]	0.486[e]
Diarrhea	518 (9.2)	317 (9.58)	239 (9.86)	1 (5.26)	1.000[e]	1.000[e]	1.000[e]
Complete blood cell count							
Hemoglobin, median g/dL, IQR	13.3 (12.2, 14.4)	12.9 (11.9, 13.6)	13.8 (12.8, 15.1)	12.3 (11.4, 13.3)	0.006[f]	0.136[f]	< 0.001[f]
Hematocrit, median %, IQR	39.2 (36.4, 42.4)	38.1 (35.6, 40.4)	41 (38, 44.1)	36 (34.6, 39.5)	0.005[f]	0.096[f]	< 0.001[f]
Lymphocyte, median %, IQR	28.9 (21.3, 36.5)	30.1 (22.8, 37.3)	30.7 (24, 37.7)	18.9 (17.2, 30.5)	0.003[f]	< 0.001[f]	< 0.001[f]
Platelets, median × 10^3/μL, IQR	228 (180, 284)	236 (188, 293)	238.5 (197, 285)	238 (223, 287)	0.056[f]	0.158[f]	0.167[f]
White blood cell, median count/μL, IQR	5,695 (4,450, 7,170)	5,660 (4,390, 7,140)	5,640 (4,425, 7,080)	7,740 (6,410, 9,300)	< 0.001[f]	< 0.001[f]	< 0.001[f]

BMI = body mass index, COVID-19 = coronavirus disease-19, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.
[a]Comparison between pregnant women and total patients except pregnant women; [b]Comparison between pregnant women and non-pregnant women; [c]Comparison between pregnant women and women aged 20–49 years except pregnant women; [d]χ^2 test was used for testing; [e]Fisher's exact test was used for testing; [f]Mann-Whitney U test (Wilcoxon two-sample test) was used for testing.

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Meanwhile, significant differences were observed in the CBC results between pregnant women and non-pregnant women: hemoglobin (g/dL) [median (IQR); 12.3 (11.4–13.3) vs. 13.8 (12.8–15.1), $P < 0.001$], white blood cell (WBC) count (cells/μL) [7,740 (6,410–9,300) vs. 5,640 (4,425–7,080), $P < 0.001$], and lymphocyte (%) [18.9 (17.2–30.5) vs. 30.7 (24.0–37.7), $P < 0.001$].

This observational multicenter study demonstrated that all 19 pregnant women with confirmed COVID-19 did not exhibit worsening of disease compared with that in non-pregnant women. To our knowledge, this is the first study to compare the morbidity and mortality rates of COVID-19 pregnant women with those of non-pregnant women of childbearing age in the ROK. Focusing on the clinical impact of COVID-19 during pregnancy can aid physicians and policy-makers in the rational prioritization of COVID-19 vaccination strategies and improving the management of COVID-19 cases. Specifically, the clinical data of domestic groups at higher risk for COVID-19 are critical for improving national preparedness and response.

Previous research provided contradictory findings regarding the increased risk for critical illness and mortality resulting from COVID-19 during pregnancy. The physiologic and immunologic changes that occur during pregnancy may increase pregnant women's vulnerability to severe infection. Previous studies suggested that pregnancy is associated with severe or critical COVID-19.[9-12] Considering the mortality rate in pregnant women with COVID-19 described in a Brazilian study, the effect of comorbid conditions and the specific viral strain may be more significant than the pregnancy status in determining clinical severity.[13] Previous observational studies noted that majority of pregnant patients do not experience severe or critical COVID-19.[6,14-23] Sentilhes et al.[24] reported that maternal age, obesity, hypertension, or diabetes may increase the risk in pregnant women with COVID-19. Because none of the pregnant women included in our study had comorbidities, further analysis in this regard was not possible.

In previous studies, the clinical outcomes associated with COVID-19 did not appear to be worse in pregnant women compared with those in the general population.[6,14-23] However, data are still limited and the sex disparities in clinical severity and mortality of COVID-19 may be a result of the sex differences in comorbidities and behaviors. Men with COVID-19 appear to have worse clinical outcomes than those in women with COVID-19.[25-28] Furthermore, older age is strongly associated with increased mortality in COVID-19 patients.[28-30] Considering that women have better outcomes than those in men,[27,28] the hormonal profile and associated physiologic changes in young pregnant women may prevent worsening of the disease. However, the physiologic reserves and immunity are reduced in this patient group.

Conflicting studies suggest that COVID-19 during pregnancy may or may not lead to an increased risk of pregnancy complications such as preeclampsia, preterm birth, miscarriage, and perinatal death.[17,19,21,31-34] Numerous factors including medical comorbidities, physiologic changes in pregnancy, and baseline susceptibility to infection in addition to social factors such as limited access to care and difficulties with social isolation may negatively impact both maternal and fetal outcomes. Further studies among Korean patients are required to explain the outcomes observed in our population.

In women with normal pregnancy, the leukocyte count was higher and the lymphocyte percentage was lower among pregnant women with COVID-19 than that among non-pregnant controls. A previous meta-analysis demonstrated a significant correlation between increased leukocyte count and decreased lymphocyte count among patients with severe cases of COVID-19 compared with those with mild cases.[35] However, these laboratory findings may

not be associated with worsening disease, but may result from other benign processes. In severe cases of COVID-19, intensive inflammation may lead to destruction of lymphatic tissues, lymphocyte apoptosis, and direct lymphocyte infection, in addition to lymphocyte inhibition due to metabolic disorders, including lactic acidosis.[36] On the contrary, pregnancy may cause immunomodulation resulting in the recognition and destruction of similar self-antigens.

During the initial stage of the pandemic, pregnant women in the ROK were hospitalized and managed according to the national policy requiring inpatient isolation, unlike other countries. These measures were implemented to prevent the lack of prenatal care, surveillance, and adequate treatment for those with COVID-19. This policy may explain why the severity of infection was similar in pregnant and non-pregnant patients.

Our study has several limitations. This analysis only included a very small number of pregnant women who did not have underlying diseases or complications associated with pregnancy. Furthermore, our study did not investigate the delivery mode, gestational age at the time of delivery, and frequency of vertical transmission or neonatal outcomes due to the limited data extracted from the government-operated registry.

In conclusion, pregnant women with COVID-19 infection were not at higher risk of severe or critical disease that would require supplemental oxygen, ICU admission, or mechanical ventilation. None of the pregnant women in our cohort experienced severe infection sequelae including sepsis, multiple organ failure, or maternal mortality. However, further analysis of multinational pregnancy cohorts is warranted to improve our understanding and strategies of managing COVID-19 in pregnant women.

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital (IRB no. 2020AN0408). The need for obtaining informed consent was waived due to the retrospective nature of the study.

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