

Clinical characteristics and outcomes of COVID-19 in pregnant women: a propensity score matched analysis of the data from the COVID-19 Registry Japan

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Summary:

Propensity score matched analysis showed that pregnancy could be a risk factor for moderate-to-severe COVID-19 in Japan. In addition to presence of comorbidities, later gestational age may be associated with severity of COVID-19 in pregnant women.

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Abstract

Background: Several studies have investigated whether pregnancy is a risk factor for developing severe COVID-19; however, the results remain controversial. In addition, the information regarding risk factors for developing severe COVID-19 in pregnant women is limited.

Methods: A retrospective cohort study analyzing the data from the nationwide COVID-19 registry in Japan was conducted. Propensity score matched analysis was performed to compare COVID-19 severity between pregnant and nonpregnant women. Multivariate analysis was also conducted to evaluate risk factors for developing moderate-to-severe COVID-19 in pregnant women.

Results: During the study period, 254 pregnant and 3752 nonpregnant women of reproductive age were identified. After propensity score matching, 187 pregnant women and 935 nonpregnant women were selected. A composite outcome of moderate-to-severe COVID-19 was more frequently observed in pregnant women than that of nonpregnant women (n=18, 9.6% vs. n=46, 4.9%; $P=0.0155$). In multivariate analysis, the presence of underlying diseases and being in the second-to-third trimester of pregnancy were recognized as risk factors for moderate-to-severe COVID-19 in pregnant women (odds ratio [95% confidence interval]: 5.295 [1.21-23.069] and 3.871 [1.201-12.477], respectively).

Conclusions: Pregnancy could be a risk factor for moderate-to-severe COVID-19 for women in Japan. In addition to the presence of comorbidities, advanced pregnancy stages may contribute to greater risks for developing moderate-to-severe COVID-19 in pregnant women.

Keywords: pregnant women; coronavirus disease 2019; severe acute respiratory syndrome coronavirus 2; propensity score matched analysis

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Abbreviations:

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVIREGI-JP, COVID-19 Registry Japan

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Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has circulated worldwide. As of September 2021, over 230 million COVID-19 cases and 4.5 million deaths were reported globally [1]. To date, many risk factors for severe illness, including increasing age, smoking, obesity, and other comorbidities, have been reported [2-6]. There have been several reports that investigated whether pregnancy is a risk factor for severe COVID-19. Easter et al. reported that intensive care unit (ICU) and hospital stay length, need for mechanical ventilation, and the frequency of acute organ injury were similar between pregnant and nonpregnant women, and all pregnant women survived [7].

In contrast, other publications, including systematic reviews, report that pregnant women tended to develop more severe COVID-19 than nonpregnant, age-matched women of reproductive age [8-11]. Because the clinical, epidemiological characteristics, and outcomes of COVID-19 appear to vary by ethnicity, other population characteristics, and regions, likely impacting the analysis of pregnant women [12, 13], the investigation in a specific population, such as Japanese in this case, might be important. In addition, the clinical information regarding the risk factors for developing severe COVID-19 in pregnant women is still limited.

In Japan, a nationwide COVID-19 registry named COVID-19 Registry Japan (COVIREGI-JP) has been in operation to collect the information of hospitalized COVID-19 patients [2]. This registry includes information regarding pregnant and nonpregnant women with COVID-19. Therefore, the primary aim of this study is to investigate whether pregnancy could be a risk factor for moderate-to-severe COVID-19 by comparing pregnant and nonpregnant women in Japan. The secondary aim is to explore risk factors for developing moderate-to-severe COVID-19 in pregnant women.

Patients and methods

Study design and setting

This study was a retrospective cohort study that analyzed the data from COVIREGI-JP, the largest, ongoing prospective inpatient COVID-19 registry data in Japan. The details of COVIREGI-JP have been reported previously [2]. In brief, this is a nationwide COVID-19 registry in which hospitalized patients with SARS-CoV-2 proven by positive nucleic amplification or antigen tests were enrolled.

Pregnant women with COVID-19 who registered in the COVIREGI-JP were included in the study. Nonpregnant female COVID-19 patients at the ages of 15 to 44 years were selected as a control group.

Outcomes

For the primary aim to compare the severity of pregnant and nonpregnant women with COVID-19, two composite outcomes were defined. Death, need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or ICU admission was set as the composite outcome for severe COVID-19. In addition, (1) the requirement of non-invasive oxygen supports, including nasal cannula, face mask, reservoir mask, high-flow oxygen device, biphasic positive airway pressure (BiPAP), and continuous positive airway pressure (CPAP) and (2) clinical condition at the time of admission, as follows, respiratory rate $\geq 24/\text{min}$, oxygen saturation $\leq 94\%$ on ambient air, or need of supplemental oxygen administration were added for composite outcome of moderate-to-severe COVID-19 according to the definition of the previous study [2]. Symptoms not fulfilling either criteria of severe or moderate-to-severe COVID-19 were all defined as mild.

Similarly, for the secondary aim to explore the risk factors for developing moderate-to-severe COVID-19 amongst pregnant women, the composite outcome of moderate-to-severe COVID-19 was used.

Statistical analysis

Categorical and continuous variables were described as number and percent and median and interquartile range, respectively. Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables were used for univariate analysis. To compare the composite outcomes between pregnant and nonpregnant women, we analyzed two groups by using Fisher's exact test with propensity score matching. Propensity scores were calculated by logistic regression analysis using known risk factors for severe COVID-19, including age, underlying diseases (cardiovascular diseases, respiratory diseases, diabetes mellitus, hypertension, hyperlipidemia, obesity, severe renal diseases or dialysis, immunosuppressive condition), and days from symptom onset to admission as covariates. One pregnant woman to five nonpregnant women (1:5) propensity score matching was performed using the nearest neighbor matching with a caliper width of 0.2 without replacement. The standardized difference was used to measure covariate balance, and a standardized mean difference above 10% was interpreted as a meaningful imbalance. In addition, a comparison of patients' backgrounds between moderate-to-severe and mild COVID-19 in pregnant women was conducted by multivariate logistic regression analysis to explore the risk of developing moderate-to-severe COVID-19 in pregnant women. A two-sided *P* value of < 0.05 was considered statistically significant. All statistical analysis was performed by R statistical software version 4.0.5.

Ethics consideration

The National Center for Global Health and Medicine (NCGM) and the National Center for Child Health and Development (NCCHD) ethics committees approved the study (NCGM-G-003494-0 and NCCHD-2020-364), respectively.

Results

Description of the entire cohort

A total of 37,138 hospitalized COVID-19 patients were registered in the COVIREGI-JP from January 2020 to April 2021. Among them, 254 pregnant and 3752 nonpregnant women of reproductive age were identified (**Figure 1**). The characteristics of pregnant and nonpregnant women in the entire cohort are shown in **Table 1**. Among pregnant women, the median (interquartile range [IQR]) age was 30.5 (26.0-35.0) years. Median gestational age was 22.0 (13.0-31.0) weeks, and 66 (26.0%) were in the first trimester, 98 (38.6%) were in the second trimester, and 87 (34.3%) were in the third trimester. In the entire cohort, 14.9% of patients had underlying diseases, and there were fewer patients with underlying disease in the pregnant women group than in nonpregnant women: 7.9% vs. 15.3% ($P=0.001$). Regarding COVID-19 exposure prior to admission, apparent close contact history was more common in pregnant women than in nonpregnant women (64.6% vs. 56.8%, $P=0.018$). The most common COVID-19 exposure in pregnant women occurred through their family, followed by their workplace. In contrast, presence of three Cs (close contact in a closed, crowded environment) was less common in pregnant women.

Clinical interventions, complications, and outcomes for pregnant and nonpregnant patients are shown in **Supplemental Table 1**. Rates of non-invasive oxygen support (5.1% vs. 4.3%,

$P=0.523$), invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (1.2% vs. 0.3%, $P=0.076$) were not statistically different. For pharmacotherapy, the frequency of using remdesivir and systemic steroids was similar; however, anticoagulant was more frequently used in the pregnant women group (9.8% vs. 2.6%, $P<0.001$) and favipiravir was less frequently used in the pregnant women group (1.2% vs. 9.7%, $P<0.001$). In the pregnant women group, one patient died.

Propensity score matched cohort

The basic characteristics of pregnant and nonpregnant women after propensity score matching are shown in **Supplemental Table 2**. After propensity score matching, 187 pregnant women and 935 nonpregnant women were selected. Patients' backgrounds, including age, underlying diseases, and days from symptom onset to admission, were acceptably similar between pregnant and nonpregnant women groups.

Only one case among pregnant women, and four cases among non-pregnant women were categorized as severe COVID-19, making it difficult to validly compare the rates. Therefore, we compared only composite outcome for moderate-to-severe COVID-19. In this analysis, the composite outcome with moderate-to-severe COVID-19 was more frequently observed in pregnant women than in nonpregnant women ($n=18$, 9.6% vs. $n=46$, 4.9%; $P=0.0155$).

Differences between moderate-to-severe and mild COVID-19 in pregnant women

Several potential risk factors for severe COVID-19 in pregnant women were assessed by comparing moderate-to-severe to mild COVID-19 pregnant patients (**Table 2**). Median gestational age was higher in the moderate-to-severe symptom group than in the mild

symptom group (29.0 vs. 20.5 weeks). More pregnant women were in their second-to-third trimesters in the moderate-to-severe symptom group ($P=0.006$). In addition, the proportion of patients with any underlying disease was higher in the moderate-to-severe symptom group than in the mild group (16.7% vs. 4.9%, $P=0.028$). In multivariate analysis, the presence of underlying diseases and being in the second-to-third trimester of pregnancy were recognized as risk factors for moderate-to-severe COVID-19 in pregnant women (odds ratio [95% confidence interval]: 5.295 [1.21-23.069] and 3.871 [1.201-12.477], respectively) (**Table 3**).

Discussion

This study revealed the potential risk for developing moderate-to-severe COVID-19 in pregnant women compared to female patients of reproductive age in Japan. It is also suggested that advanced gestational stage including the second-to-third trimester may be associated with moderate-to-severe COVID-19 in pregnant women.

The risk of developing severe COVID-19 during pregnancy has been evaluated in various regions and countries, with conflicting results. Several case-control and retrospective cohort studies performed in the United States [8] and Mexico [9] revealed that pregnancy could be a risk factor for developing a severe form of COVID-19. In addition, some systematic reviews and meta-analyses have shown similar results [10, 11]. On the other hand, some systematic reviews showed no difference in the outcomes of pregnant women compared to nonpregnant women [14, 15]. Our results support previous reports that pregnant women could be at a higher risk of severe COVID-19. Although the reasons for these conflicting results are still unclear, in addition to differences in ethnicity and health care systems, the timing of each study and differences in the prevalent strains at the research site may have had an impact on the results. Furthermore, the definition of severe COVID-19 in pregnant women in each study

may also affect the result. In our study, only composite outcome with moderate-to-severe COVID-19 could be evaluated and showed statistical differences. Several definitions of COVID-19 severity are used in various studies. For example, Oakes et al. used Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERET) and the World Health Organization Ordinal Scale for Clinical Improvement (WHOOSCI) criteria for the definition of severe COVID-19 in pregnant women in their study. These criteria are non-admission-based clinical criteria [8]. In contrast, Martinez-Portilla et al. used death, pneumonia, intubation, and ICU admission as their outcome to assess severe COVID-19 [9]. Establishing a standardized (widely accepted) definition of severe, moderate, and mild COVID-19 in pregnant women may be necessary to generalize the risk factors for pregnant women across the studies.

In addition, pregnancy in the second-to-third trimesters and any underlying diseases were more commonly seen in moderate-to-severe COVID-19 patients than in mild disease patients. Allotey et al. showed that higher maternal age, high body mass index, and several underlying conditions were associated with severe COVID-19, whereas the gestational age at the onset of disease was not [10]. In their systematic review, Lassi et al. showed that pregnant women with obesity, smoking history, diabetes, and pre-eclampsia were at a higher risk for severe COVID-19. However, the majority of pregnant women included in this review were in their third trimester. Thus, the association between COVID-19 severity and the stage of pregnancy was not fully evaluated [16]. Our study suggests that being in the second-to-third trimester could be a risk factor for developing moderate-to-severe COVID-19 in pregnant women. This phenomenon has been observed in influenza infection [17]. It is theoretically understandable because numerous physiological changes during pregnancy, such as increased body fluid in the third space and compromised immune system due to the need for immune tolerance for the fetus, develop as a pregnancy advances [18].

Treatment strategies for COVID-19 in pregnant women have not yet been established as there is limited information on remdesivir [19], antibody cocktail [20], and other therapeutic agents for COVID-19 in pregnant women. If pregnancy itself is a risk factor for moderate-to-severe COVID-19, pregnant women may benefit from proactive treatment, and our results may be important in considering which specific therapeutic agents should be used for pregnant patients. For example, antibody cocktail is currently used only for pregnant women in the third trimester with COVID-19 in Japan. However, our results may indicate that patients in their second trimester could benefit from the early administration of antibody cocktail treatment to prevent the development of moderate-to-severe COVID-19.

Because COVID-19 in pregnant women could be severe and occasionally life-threatening, prevention is also essential. A previous study conducted in the early phase of the COVID-19 pandemic in Japan revealed that approximately 60% of the hospitalized patients with COVID-19 had close contact with COVID-19 cases prior to hospitalization [2]. The detailed sources of infection for pregnant women who contract COVID-19 are not known. In the current study, the exposure from family members with COVID-19 was more frequently seen in pregnant women than that in nonpregnant women. In addition, the presence of the three Cs (close contact in a closed crowded space) was lower in pregnant women than that in nonpregnant women. This indicated that pregnant women refrain from going out or adhere more strictly to self-hygiene behaviors outside, although avoiding household transmission may be more difficult. Therefore, family members of pregnant women should be compliant with COVID-19 preventive measures, including vaccination, wearing masks, avoiding crowds and poorly ventilated spaces, and keeping physical distancing as much as possible [21]. As the efficacy of the SARS-CoV-2 vaccine has become more evident, it is crucial for pregnant women to receive the SARS-CoV-2 vaccine to prevent themselves from contracting COVID-19. Fortunately, there has been no significant safety concern regarding COVID-19

vaccines in pregnant women as of today [22, 23], and vaccines have been widely distributed worldwide [24]. Importantly, however, this study was conducted before the SARS-CoV-2 vaccine was widely distributed in Japan, and we could not assess the vaccine efficacy among pregnant women.

This study has several limitations. First, although COVIREGI-JP is the largest COVID-19 registry in Japan, it does not contain information on perinatal outcomes. Therefore, we could only evaluate the outcomes of pregnant women, but not the fetus or newborns. Second, we could not access the information regarding the SARS-CoV-2 variant strains; therefore, we were unable to evaluate the effect of variant strain on the maternal outcome. During the study period between January 2020 to April 2021, the alpha variant of concern (VOC) had been circulating as the major VOC in Japan. The alpha VOC had increased from December 2020 and it was the predominant strain until July 2021 [25]. Afterwards, the delta VOC had become predominant. The coverage of our data was until April 2021, and therefore, the effect of the delta VOC was negligible. Third, the association between underlying diseases and worse outcomes within pregnant women appears to be driven by diabetes mellitus; however, it was not possible to assess the effect of diabetes mellitus directly because of the small patient number. Further analysis using a population sample with more diabetic patients is needed to clarify this issue. Fourth, the current study included only hospitalized patients, and therefore, our results would not necessarily apply to the outpatient setting. Lastly, we were unable to assess the relationship between severe COVID-19 and pregnancy because of the small number of patients with severe COVID-19.

In conclusion, pregnancy could be a risk factor for moderate-to-severe COVID-19 amongst women of reproductive age in Japan, and the risk may be greater during the second-to-third trimester of pregnancy. However, our assessment was limited by the lack of severe cases and a further large-scale study is required to investigate perinatal outcomes in this population.

NOTES

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Table 1. Patient background (entire cohort)

Variables, number (%) or median [IQR]	Subcategories	Total	Pregnant women	Non-pregnant women	<i>P</i> [†]
Case number		4006	254	3752	NA
Age, years, median [IQR]		29.0 [24.0-37.0]	30.5 [26.0-35.0]	29.0 [23.0-37.0]	0.121
Age category	15 to < 35 years	2744 (68.5)	189 (74.4)	2555 (68.1)	0.036
	35 to < 45 years	1262 (31.5)	65 (25.6)	1197 (31.9)	
Body weight, kg, median [IQR]		53.8 [48.6-60.7]	57.0 [51.1-63.0]	53.0 [48.0-60.0]	< 0.001
Ethnicity	Japanese	3574 (89.2)	219 (86.2)	3355 (89.4)	0.116
	Non-Japanese Asian	260 (6.5)	26 (10.2)	234 (6.2)	
	Others	96 (2.4)	5 (2.0)	91 (2.4)	
	Unknown	76 (1.9)	4 (1.6)	72 (1.9)	
Smoking history	Currently smoking	644 (16.1)	13 (5.1)	631 (16.8)	< 0.001
	Past smoking	304 (7.6)	31 (12.2)	273 (7.3)	
	Never	2533 (63.2)	159 (62.6)	2374 (63.3)	
	Unknown	525 (13.1)	51 (20.1)	474 (12.6)	
Gestational age category		NA		NA	NA
1st trimester (0 to < 14 weeks)			66 (26.0)		
2nd trimester (14 to < 28 weeks)			98 (38.6)		
3rd trimester (≥ 28 weeks)			87 (34.3)		
Unknown			3 (1.2)		
Underlying diseases	Any	595 (14.9)	20 (7.9)	575 (15.3)	0.001
	Bronchial asthma	263 (6.6)	10 (3.9)	253 (6.7)	0.088
	Obesity	144 (3.6)	3 (1.2)	141 (3.8)	0.034
	Diabetes mellitus	80 (2.0)	4 (1.6)	76 (2.0)	0.817
	Hypertension	59 (1.5)	2 (0.8)	57 (1.5)	0.585
	Hyperlipidemia	42 (1.0)	0 (0.0)	42 (1.1)	0.11
	Solid tumor	36 (0.9)	0 (0.0)	36 (1.0)	0.168
	Collagen disease	24 (0.6)	1 (0.4)	23 (0.6)	1
	Mild liver disease	19 (0.5)	0 (0.0)	19 (0.5)	0.629
	Others	72 (1.8)	1 (0.4)	71 (1.9)	0.088
Immunosuppressive condition		50 (1.2)	0 (0.0)	50 (1.3)	0.073

Exposure within 14 days prior to admission	Close contact with COVID-19 cases*	2297 (57.3)	164 (64.6)	2133 (56.8)	0.018
	Family	844 (21.1)	100 (39.4)	744 (19.8)	< 0.001
	Educational facility	66 (1.6)	3 (1.2)	63 (1.7)	0.798
	Healthcare facility	296 (7.4)	6 (2.4)	290 (7.7)	0.001
	Nonfamily roommates	101 (2.5)	7 (2.8)	94 (2.5)	0.835
	Workplace	697 (17.4)	32 (12.6)	665 (17.7)	0.04
	Others	445 (11.1)	20 (7.9)	425 (11.3)	0.098
Presence of “three Cs” (close contact in a closed crowded space)		801 (20.5)	21 (8.3)	780 (21.4)	< 0.001
Days of hospitalization from symptom onset, median [IQR]		4.0 [2.0-7.0]	4.0 [2.0-6.0]	4.0 [2.0-7.0]	0.604

IQR, interquartile range; NA, not applicable. *Duplication is allowed.

†For categorical and continuous variables, Fisher’s exact test and Mann-Whitney *U* test were used, respectively.

Table 2. Comparison between moderate-to-severe and mild COVID-19 in pregnant women

Variables	Case number	Subcategories	Moderate-to-severe symptoms	Mild symptoms	<i>P</i> *
Case number	254		30	224	
Age, years, median [IQR]	254		32 [27-34]	30 [26-35]	0.602
Age category, number (%)	254	15 to < 35 years	23 (76.7)	166 (74.1)	1.0
		35 to < 45 years	7 (23.3)	58 (25.9)	
Smoking history	203	Currently smoking	1 (3.3)	12 (5.4)	0.553
		Past smoking	6 (20.0)	25 (11.2)	
		Never	17 (56.7)	142 (63.4)	
		Unknown	6 (20.0)	45 (20.1)	
Gestational age, weeks, median [IQR]	251		29 [24-34]	20.5 [12-30]	
Gestational age category	251				0.006
1st trimester (0 to < 14 weeks)			2 (6.9)	64 (28.8)	
2nd trimester (14 to < 28 weeks)			10 (34.5)	88 (39.6)	
3rd trimester (≥ 28 weeks)			17 (58.6)	70 (31.5)	
Underlying diseases*, number (%)	254	Any	5 (16.7)	11 (4.9)	0.028
		Bronchial asthma	2 (6.7)	8 (3.6)	0.335
		Obesity	0 (0.0)	3 (1.3)	1.0
		Diabetes mellitus	3 (10.0)	1 (0.4)	0.005
		Leukemia	1 (3.3)	1 (0.4)	0.223
		Collagen disease	0 (0.0)	1 (0.4)	1.0

*Results of Fisher's exact test for categorical variables and Kruskal-Wallis test (Mann-Whitney *U* test) for continuous variables.

IQR, interquartile range

Table 3. Results of multivariate logistic regression analysis including the trimester of pregnancy, age, and comorbidities (pregnant women only)

Variable	Odds ratio	95% confidence interval	<i>P</i>
Second-to-third trimester of pregnancy	5.295	1.215-23.069	0.026
Age	1.014	0.945-1.087	0.705
Any comorbidity	3.871	1.201-12.477	0.023

Figure Legends

Figure 1. Patient selection flow diagram.

Figure 1

