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Journal of Infection and Chemotherapy 29 (2023) 33–38

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Comparison of clinical characteristics of COVID-19 in pregnant women between the Delta and Omicron variants of concern predominant periods

Kensuke Shoji [a,*], Shinya Tsuzuki [b,c], Takayuki Akiyama [b], Nobuaki Matsunaga [b], Yusuke Asai [b,c], Setsuko Suzuki [c], Noriko Iwamoto [b,c], Takanori Funaki [a], Masaki Yamada [a,d], Nobuaki Ozawa [e], Koushi Yamaguchi [e], Isao Miyairi [a,f], Norio Ohmagari [b,c]

[a] Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan
[b] AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan
[c] Department of Infectious Diseases, Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan
[d] Department for Advanced Medicine for Viral Infections, National Center for Child Health and Development, Tokyo, Japan
[e] Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan
[f] Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

ARTICLE INFO

Keywords:
Pregnant women
Coronavirus disease 2019
Severe acute respiratory syndrome coronavirus 2
Variant of concern

ABSTRACT

Background: Information regarding effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant strains on clinical manifestations and outcomes of coronavirus disease 2019 (COVID-19) in pregnant women is limited.

Methods: A retrospective observational study was conducted using the data from the nationwide COVID-19 registry in Japan. We identified pregnant patients with symptomatic COVID-19 hospitalized during the study period. The Delta and Omicron variants of concern (VOC) predominant periods were defined as August 1 to December 31, 2021 and January 1 to May 31, 2022, respectively. Clinical characteristics were compared between the patients in the Delta and Omicron VOC periods. In addition, logistic regression analysis was performed to identify risk factors for developing moderate-to-severe COVID-19.

Results: During the study period, 310 symptomatic COVID-19 cases of pregnant women were identified; 111 and 199 patients were hospitalized during the Delta and Omicron VOC periods, respectively. Runny nose and sore throat were more common, and fatigue, dysgeusia, and olfactory dysfunction were less common manifestations observed in the Omicron VOC period. In the multivariable logistic regression analysis, onset during the later stage of pregnancy (OR: 2.08 [1.24–3.71]) and onset during the Delta VOC period (OR: 2.25 [1.08–4.90]) were independently associated with moderate-to-severe COVID-19, whereas two doses of SARS-CoV-2 vaccine were protective against developing moderate-to-severe COVID-19 (OR: 0.34 [0.13–0.84]).

Conclusions: Clinical manifestations of COVID-19 in pregnant women differed between the Delta and Omicron VOC periods. SARS-CoV-2 vaccination was still effective in preventing severe COVID-19 throughout the Delta and Omicron VOC periods.

1Introduction

Coronavirus disease 2019 (COVID-19) continues to be a major problem worldwide. Over 500 million cases and 6 million deaths were reported as of June 2022 [1]. Along with the spread of the COVID-19 pandemic, reports of COVID-19 in pregnant women have increased [2,3]. It has been reported that pregnant women are more susceptible to severe COVID-19 than non-pregnant women, particularly in the second and third trimester of pregnancy [4–6]. It is also known that premature births increase in pregnant women with COVID-19 [7,8].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, can easily mutate, and many variant strains have

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variants of concern; COVIREGI-JP, COVID-19 Registry Japan.

* Corresponding author. Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Okura, Setagaya-ku, Tokyo, 157-8535, Japan.
E-mail address: shoji-k@ncchd.go.jp (K. Shoji).

https://doi.org/10.1016/j.jiac.2022.09.005
Received 23 July 2022; Received in revised form 2 September 2022; Accepted 6 September 2022
Available online 11 September 2022

arisen so far. Of these, clinically and epidemiologically important strains are categorized as variants of concern (VOC), including the Delta and Omicron VOC [9]. The Delta VOC has been reported to be more infectious and cause more severe COVID-19 than the conventional variant strains [10,11]. The Omicron VOC, which emerged later, is even more contagious than the Delta VOC, but its severity is reported to be lower [12,13]. Furthermore, the effectiveness of the SARS-CoV-2 vaccines has decreased against the Omicron VOC [14,15]. As such, the impact of the predominant variant strains on the clinical characteristics of COVID-19 in the general population is now fairly well understood. It has also been reported that clinical characteristics, such as severity of COVID-19, may differ by ethnicity or socioeconomic factors [16,17]; therefore, it is important to evaluate data regarding the clinical characteristic of COVID-19 in pregnant women from different countries and regions. However, the information regarding the characteristics of maternal COVID-19 during the Delta and Omicron VOC periods is very limited [12,18].

Therefore, we conducted this study to clarify the differences in clinical characteristics of COVID-19 in pregnant women between the Delta and Omicron VOC periods in Japan.

2Patients and methods

2.1Study design, patient population, and purposes of the study

This study is a retrospective observational study using the data from the COVID-19 registry Japan (COVIREGI-JP), the largest nationwide COVID-19 registry in Japan. The details of COVIREGI-JP were described previously [19]. Briefly, 706 institutions across Japan have participated and enrolled 70,000 patients as of June 2022 [20]. Laboratory diagnosed, hospitalized COVID-19 patients in all age groups were included. This study identified from this registry the pregnant patients with symptomatic COVID-19 hospitalized between August 1, 2021 to March 31, 2022. The Delta and Omicron VOC periods were defined as August 1 to December 31, 2021 and January 1 to May 31, 2022, respectively. Information regarding patients' backgrounds and clinical characteristics, including age, gestational age, SARS-CoV-2 vaccination history, prior exposure to COVID-19 before admission, signs and symptoms at admission, clinical course, treatment, and outcomes were extracted from the database. Asymptomatic cases were excluded from the analyses.

The primary purpose of the study was to describe the clinical and epidemiological differences of COVID-19 in symptomatic pregnant women hospitalized between the Delta and Omicron VOC predominant periods. The secondary purpose was to assess the effect of SARS-CoV-2 vaccination and the type of predominant variant strains on COVID-19 severity.

2.2Definition of outcomes

In this study, patients were divided into two groups, namely, the mild and moderate-to-severe groups. The moderate-to-severe group was defined as the presence of one or more of the following [4]: clinical condition at the time of admission (respiratory rate $\geq$ 24 breaths/minute or oxygen saturation $\leq$ 94% on ambient air, or need of supplemental oxygen administration), the requirement of noninvasive oxygen supports (including nasal cannula, face mask, reservoir mask, high-flow oxygen device, biphasic positive airway pressure, and continuous positive airway pressure), need for mechanical ventilation, need for extracorporeal membrane oxygenation (ECMO), intensive care unit (ICU), and death. The patients who did not meet these criteria were categorized as mild.

2.3Statistical analysis

Categorical variables were described as numbers and percentages, and continuous variables were described as median and interquartile range (IQR). To compare two groups, the chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables were used as univariable analysis. To determine the risk factors for developing moderate-to-severe COVID-19, a logistic regression analysis was performed. In addition to SARS-CoV-2 vaccination history and type of VOC, potential confounders including age, gestational age, underlying diseases, and smoking history were entered as covariates. In addition to the total cohort analysis, a subgroup analysis including only patients during the Omicron VOC period was performed to investigate the characteristics of the latest circulating Omicron strain alone, which has been associated with less severe disease. The results of multivariable analysis were expressed as odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were conducted using the statistical software R version 4.1.3.

2.4Ethics

This study was performed with permission of the ethics committees of the National Center for Global Health and Medicine (NCGM-G-003494-0) and the National Center for Child Health and Development (NCCHD-2022-052).

3Results

During the study period, 14,006 COVID-19 cases were enrolled into the registry. Among them, we found 348 cases of pregnant women with COVID-19. After excluding 38 asymptomatic patients, 310 symptomatic patients were identified; 111 and 199 patients were hospitalized during the Delta and Omicron VOC periods, respectively (Fig. 1). Patient characteristics are summarized in Table 1. The median (IQR) age was 30 (26–35). The numbers and percentages of infections that occurred during the first, second, and third trimesters were 40 (13.0%), 98 (31.9%), and 169 (55.0%), respectively. The most common underlying disease was bronchial asthma (n = 17, 5.5%), followed by obesity (n = 10, 5.5%) and diabetes mellitus (n = 6, 1.9%). Exposure within 14 days prior to admission was recognized in 197 (64.0%), and more than half of the patients contracted COVID-19 from their family (n = 158, 51.0%). These characteristics were similar between the Delta and Omicron VOC periods. For the SARS-CoV-2 vaccination history, 132 (42.6%) patients had received two doses of SARS-CoV-2 vaccine, and the majority of these patients were hospitalized in the Omicron VOC period (n = 4, 3.6% in the Delta VOC period and n = 128, 64.3% in the Omicron VOC period).

The incidence of symptoms at hospitalization during these periods is shown in Fig. 2. Runny nose (P = 0.047) and sore throat (P = 0.028) were more common, and fatigue (P = 0.026), dysgeusia (P < 0.001), and olfactory dysfunction (P < 0.001) were less common in the Omicron VOC period than in the Delta VOC period.

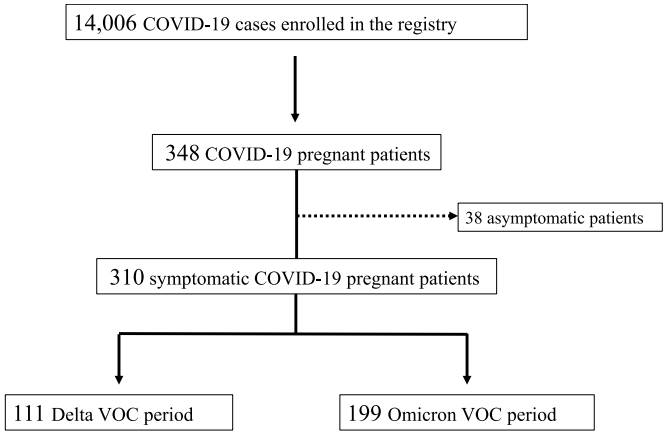

Fig. 1. Patient selection flow diagram
VOC, variant of concern

Table 1
Patient characteristics.

Variables	Number of cases	Subcategory	Total	Delta VOC period	Omicron VOC period	*P* value
Case number	310			111	199	
Age (years), median (IQR)	310		30 (26–35)	31 (27–35)	30 (26–35)	0.628
Body weight, median (IQR)	301		58.0 (53.0–64.0)	57.6 (53.0–62.3)	58.0 (53.4–65.0)	0.333
Smoking history	310	Currently smoking	15 (4.8)	5 (4.5)	10 (5.0)	0.869
		Past smoking	44 (14.2)	18 (16.2)	26 (13.1)	
		Never	222 (71.6)	77 (69.4)	145 (72.9)	
		Unknown	29 (9.4)	11 (9.9)	18 (9.0)	
Gestational age category	310	1st trimester (0 to < 14 weeks)	40 (13.0)	14 (12.6)	26 (13.3)	0.807
		2nd trimester (14 to < 28 weeks)	98 (31.9)	38 (34.2)	60 (30.6)	
		3rd trimester (≥28 weeks)	169 (55.0)	59 (53.2)	110 (56.1)	
		Unknown	3 (1.1)	0 (0.0)	3 (1.5)	
Underlying disease, number (%)	310	Any underlying disease	33 (10.6)	12 (10.8)	21 (10.6)	0.999
		Bronchial asthma	17 (5.5)	7 (6.3)	10 (5.0)	0.830
		Obesity	10 (3.2)	4 (3.6)	6 (3.0)	0.999
		Diabetes mellitus	6 (1.9)	1 (0.9)	5 (2.5)	0.577
		Collagen disease	3 (1.0)	0 (0.0)	3 (1.5)	0.487
Immunosuppressive condition, number (%)	310		1 (0.3)	0 (0.0)	1 (0.5)	0.999
Exposure within 14 days prior to admission	310	Travel abroad	1 (0.3)	1 (0.9)	0 (0.0)	0.999
		Close contact with COVID-19 cases	197 (64.0)	76 (69.7)	121 (60.8)	0.218
		Family	158 (51.0)	56 (50.5)	102 (51.3)	0.986
		Educational facility	7 (2.3)	3 (2.7)	4 (2.0)	0.999
		Nonfamily roommates	4 (1.3)	2 (1.8)	2 (1.0)	0.943
		Workplace	21 (6.8)	11 (9.9)	10 (5.0)	0.160
		Healthcare facility	2 (0.6)	1 (0.9)	1 (0.5)	0.999
		Others	10 (3.2)	7 (6.3)	3 (1.5)	0.050
Number of patients with two doses of SARS-CoV-2 vaccine	310		132 (42.6)	4 (3.6)	128 (64.3)	<0.001

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory coronavirus type 2; VOC, variant of concern; IQR, interquartile range; NA, not applicable.

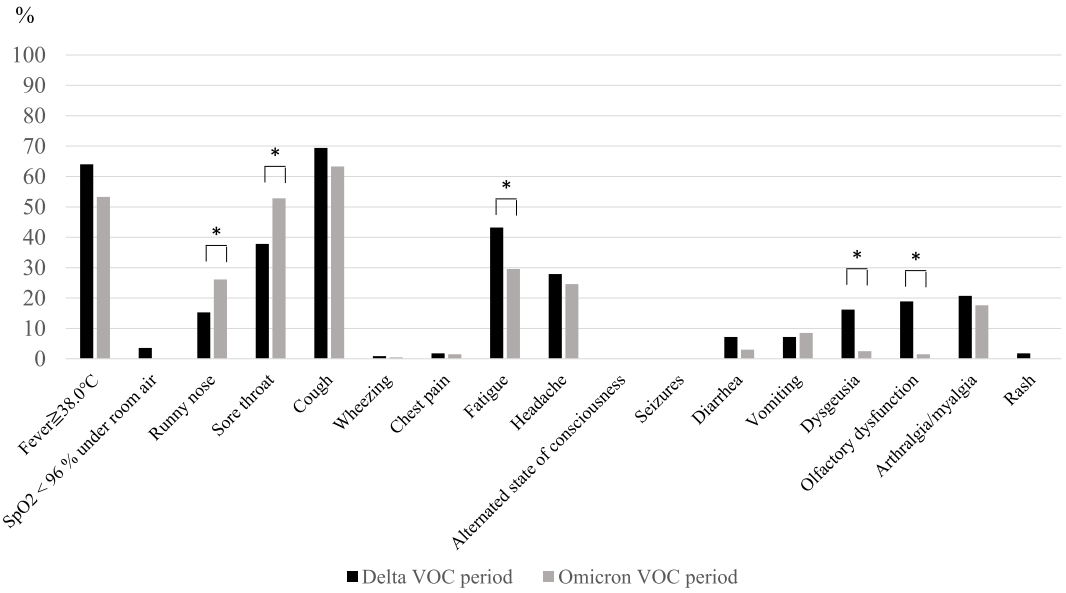

Fig. 2. Incidence of symptoms at hospitalization in the Delta and Omicron VOC periods
* indicates statistical significance
VOC, variant of concern

Among the patients, 52 (16.8%) cases required noninvasive oxygen support. The most commonly used medication type for COVID-19 was steroids (n = 41, 13.2%), followed by remdesivir (n = 27, 8.7%) and casirivimab/imdevimab (n = 4, 1.3%). For severity and outcomes, eight (2.6%) patients required ICU admission, and one patient required invasive mechanical ventilation; however, no patients died. Compared with the Delta VOC period, fewer patients in the Omicron VOC period required noninvasive oxygen support, remdesivir, or steroid administration (Table 2).

Table 3 shows the results of univariable and multivariable analyses between the mild and moderate-to-severe COVID-19 groups. In the multivariable logistic regression analysis, later stage of trimester (OR: 2.08 [1.24–3.71]) and the patients in the Delta VOC period (OR: 2.25 [1.08–4.90]) were independently associated with moderate-to-severe COVID-19, and a two-dose regimen of SARS-CoV-2 vaccine was protective for developing moderate-to-severe COVID-19 (OR: 0.34

Table 2
Comparison of severity, complications, and outcomes between the Delta variant and Omicron VOC periods.

Variables	Total	Delta VOC period	Omicron VOC period	*P* value
Number of cases	310	111	199	
Noninvasive oxygen support (nasal cannula, face mask, reservoir mask, high-flow oxygen device)	52 (16.8)	32 (28.8)	20 (10.1)	<0.001
Invasive mechanical ventilation/ECMO	1 (0.3)	0 (0.0)	1 (0.5)	0.999
Medications				
Remdesivir	27 (8.7)	21 (18.9)	6 (3.0)	0.003
Casirivimab/imdevimab	4 (1.3)	4 (3.6)	0 (0.0)	0.030
Sotorovimab	0 (0.0)	0 (0.0)	6 (3.0)	0.030
Nirmatorelvir/ritonavir	0 (0.0)	0 (0.0)	0 (0.0)	NA
Steroids	41 (13.2)	32 (28.8)	9 (4.5)	<0.001
Length of hospital stay (days), median (IQR)	8 (5–9)	8 (6–9)	8 (5–9)	0.282
ICU admission	8 (2.6)	5 (4.5)	3 (1.5)	0.222
Death	0 (0.0)	0 (0.0)	0 (0.0)	NA

VOC, variant of concern; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

[0.13–0.84]). Finally, similar analyses were performed, including a subset of patients in the Omicron VOC period (Supplemental Table 1). Later stages of gestation were still significantly associated with moderate-to-severe COVID-19 (OR: 4.10 [1.41–16.92]). The patients with moderate-to-severe COVID-19 less commonly received SARS-CoV-2 vaccinations, but this was not statistically significant (OR: 0.40 [0.15–1.03]).

4Discussion

This study revealed that the clinical characteristics of pregnant COVID-19 patients were different between the Delta and Omicron VOC periods and the overall severity was lower in the latter. In addition, later stages of pregnancy and lack of SARS-CoV-2 vaccination were associated with higher severity throughout both periods.

It is known that the characteristics of COVID-19 in the general population can be different according to the predominant SARS-CoV-2 variant strains. For example, it has been reported that the clinical manifestations of COVID-19 were different in the Delta and Omicron VOC predominant periods; sore throat was more common (70.5% vs. 60.8%) and loss of smell was less common (16.7% vs. 52.7%) in the Omicron VOC period than those in the Delta VOC period [12]. Regarding their severity, many studies showed that COVID-19 caused by the Omicron VOC was less severe than the one caused by the Delta VOC or other variant strains [12,21,22]. A report investigating the clinical characteristics of COVID-19 in pregnant women revealed that pregnant women were less likely to have fever, cough, dyspnea, and myalgia, but more likely to be admitted to the intensive care unit compared with non-pregnant women [5]. However, information regarding the effect of different variant strains on clinical manifestations and severity of COVID-19 in pregnant women has been limited. Our data showed a higher incidence of runny nose and sore throat and lower incidence of fatigue, dysgeusia, and olfactory dysfunction and milder clinical course in the Omicron VOC period than those in the Delta VOC period, which are consistent with previous reports in the general population.

Later stage of pregnancy was identified as a risk factor for developing moderate-to-severe COVID-19 for pregnant women in this study. Our research group previously reported that COVID-19 in pregnant women in the second and third trimesters were more severe than those in the first trimester using data from the COVIREGI-JP in the pre-Delta VOC period [4]. The results of the current study showed that this characteristic has not changed even in the Delta and Omicron VOC periods. This observation suggests that pregnant women, particularly in the later stage of pregnancy, should continue to take greater precautions to avoid COVID-19.

In our study, the pregnant patients who received two doses of SARS-CoV-2 vaccine were associated with milder severity of COVID-19. There have been many studies that showed efficacy in preventing SARS-CoV-2 infection, hospitalization, and death due to COVID-19 including the Delta or Omicron VOC periods [14,15,23–25]. The favorable safety and

Table 3
Univariable and multivariable analyses for identifying risk factors for moderate-to-severe COVID-19 in pregnant women.

Variables	Moderate-to-severe COVID-19 **(n = 52)**	Mild COVID-19 **(n = 258)**	OR (95% CI)		OR (95% CI)	
			Unadjusted	*P* value	Adjusted	*P* value
Age (years), median (IQR)	32 (26–34)	30 (26–35)	1.03 (0.97–1.08)	0.338	1.04 (0.98–1.10)	0.226
Currently smoking	1 (1.9)	14 (5.4)	0.34 (0.02–1.76)	0.305	0.37 (0.02–2.15)	0.360
Gestational age category						
1st trimester (0 to < 14 weeks)	1 (1.9)	39 (15.1)	2.06 (1.26–3.57)	0.006	2.08 (1.24–3.71)	0.008
2nd trimester (14 to < 28 weeks)	15 (28.8)	83 (32.2)				
3rd trimester (≥28 weeks)	36 (69.2)	133 (51.6)				
Unknown	0 (0.0)	3 (1.2)				
Underlying disease, number (%)						
Any underlying disease[a]	8 (15.4)	25 (9.7)	1.69 (0.68–3.86)	0.229	1.59 (0.60–3.90)	0.327
Bronchial asthma	4 (7.7)	13 (5.0)	1.57 (0.43–4.66)	0.447		
Obesity	3 (5.8)	7 (2.7)	2.20 (0.46–8.20)	0.266		
Diabetes mellitus	2 (3.8)	4 (1.6)	2.54 (0.35–13.38)	0.289		
Collagen disease	0 (0.0)	3 (1.2)	NA	0.987		
Number of patients with two doses of SARS-CoV-2 vaccine	9 (17.3)	123 (47.7)	0.23 (0.10–0.47)	<0.001	0.34 (0.13–0.84)	0.021
Patients in the Delta VOC period	32 (61.5)	79 (30.6)	3.63 (1.97–6.82)	<0.001	2.25 (1.08–4.90)	0.035

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory coronavirus type 2; VOC, variant of concern; IQR, interquartile range; OR, odds ratio; CI, confidential interval; NA, not applicable.

[a] Only "Any underlying disease" was entered into the multivariable analysis.

efficacy of SARS-CoV-2 vaccines in pregnant women have also been reported [26–29] and SARS-CoV-2 vaccination in pregnant women at any stage of pregnancy has been recommended worldwide, including in Japan [30–32]. Our study results in the total cohort were consistent with previous reports and demonstrated the benefits of SARS-CoV-2 vaccination in pregnant women even in the Delta and Omicron VOC periods. The subset analysis of patients in the Omicron VOC period also showed a protective trend for the vaccine, although this was not statistically significant. This is likely due to the insufficient number of patients in the Omicron VOC period, but further investigation in a larger population is warranted. In the present study, the SARS-CoV-2 vaccination coverage of pregnant women differed greatly, ranging from 3.6% in the Delta VOC period to 64.3% in the omicron VOC period. At the time of the Delta VOC period, SARS-CoV-2 vaccines had already been approved for two doses for adult population [33], and the cause of this difference is unknown. However, we speculate that the higher vaccine efficacy against the Delta VOC [14] prevented a significant proportion of hospitalizations during this period.

This study has several limitations. First, our registry did not include the outcomes of pregnancy. Therefore, we could not investigate about the association with predominant VOCs and pregnancy outcomes. Several meta-analyses revealed the negative impacts of maternal COVID-19 on pregnancy outcomes, such as increasing preterm birth, preeclampsia, and stillbirth [34,35]. However, the information regarding the effect of predominant VOCs on fetal outcomes is still limited and further study is warranted to reveal the unreported effects in Japan. Second, we had no individual data regarding the type of VOCs in our patients. Therefore, the effect of VOCs on clinical characteristics could not be assessed directly. However, surveillance data from the National Institute of Infectious Diseases indicated that more than 95% of variant strains detected in Japan during our defined Delta and Omicron VOC periods were the Delta and the Omicron VOC, respectively [36]. Therefore, we believe that the impact of the lack of sequence information for the VOCs was minimal. Lastly, as the registry only includes inpatients, it could be biased if the indications for hospitalization have changed in each period. For example, more severely ill patients may have been selectively admitted during the Omicron VOC period, when the number of patients was higher, which may have affected the interpretation of severity in both periods.

In conclusion, the clinical characteristics of COVID-19 in pregnant women differed by the period of predominant VOCs. To achieve better management of COVID-19, the information on the clinical features of COVID-19 in pregnant women should continue to be updated in preparation for any new VOC emerging in the future.

5Authorship statement

KS contributed to conceptualizing and designing the study and drafted the manuscript. ST and TA contributed to perform statistical analysis, and revising of the manuscript. NM, YA, SS, and NI contributed to data collection, and revising of the manuscript. TF, MY, N Ozawa, YI and IM contributed to the revised the manuscript. N Ohmagari contributed to the revised the manuscript, and supervised the study. All authors meet the ICMJE authorship criteria. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of competing interest

K. Shoji received payment for lectures from Mitsubishi Tanabe Pharma, Astellas, AbbVie GK, Biomerieux Japan, Nippon Becton Dickinson Company, Ltd., VIATRIS and Gilead. S. Tsuzuki received payment for supervising medical articles from Gilead Sciences, Inc. The other authors declare that they do not have any conflicts of interests directly associated with the study.

Acknowledgements

This work was partly supported by the Ministry of Health, Labour and Welfare (MHLW) Research on Emerging and Re-emerging Infectious Diseases and Immunization Program Grant Number 19HA1003 and Repository of Data and Biospecimen of Infectious Disease Program (REBIND).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.09.005.

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