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Characteristics and Outcomes of COVID-19 in Reproductive-Aged Pregnant and Nonpregnant Women in Osaka, Japan

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ABSTRACT

Objective: To describe the clinical characteristics and outcomes of reproductive-aged female patients with coronavirus disease 2019 (COVID-19).

Methods: We conducted a retrospective study of female patients aged 10–49 years, diagnosed with COVID-19 in Osaka, Japan, between January and November 2020. We assessed their epidemiological and clinical characteristics according to their pregnancy status.

Results: A total of 4,156 patients were enrolled, of whom 29 (0.7%) were pregnant. Most patients exhibited mild symptoms, and 10.8% of the cases were asymptomatic. No moderate or severe cases were observed in pregnant women, whereas only 0.1% of the nonpregnant women had severe disease at diagnosis. No clusters were observed in the pregnant patients; however, most acquired the infection from a family member. Of the 29 pregnant women, 22 (75.9%) were hospitalized; whereas among the nonpregnant women, 579 (14.0%) were hospitalized ($p < 0.001$). No patients were admitted to the intensive care unit, and there were no deaths among women aged 10–49 years.

Conclusions: Pregnant women accounted for 0.7% of the total cases of COVID-19 among women aged 10–49 years. Pregnant women were more likely to be hospitalized but generally had mild disease.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China (Li et al., 2020, Zhou et al., 2020), and rapidly spread worldwide, imposing a major burden on healthcare systems globally. Pregnant women are considered to be at a higher risk of severe morbidity and mortality from other respiratory infections, such as influenza or SARS (Allotey et al., 2020, Blitz et al., 2020, Vintzileos et al., 2020, Xu et al., 2020), than nonpregnant

women. COVID-19 has caused serious concerns about its potential to cause adverse events and poor outcomes in pregnant women. A high incidence of obstetric complications has been reported in pregnant women infected with COVID-19 (Sahin et al., 2021). Preterm delivery is the most common obstetric complication, followed by miscarriage. While the effect of COVID-19 on miscarriage has not been confirmed, the majority of previous studies have reported an increased rate of preterm delivery (Chmielewska et al., 2021, Dey et al., 2021, Sahin et al., 2021).

Concerning the immunology of SARS-CoV-2 infection in pregnant women, investigations have shown an increase in anti-SARS-CoV-2 IgM and IgG antibodies in infected pregnant women. The elevation in IgM and IgG antibodies in pregnant SARS-CoV-2-infected patients may be owing to an aggressive immunological response, including cytokine storm (Chaubey et al., 2021, Dong et al., 2020, Iyer et al., 2020). The cytokine storm is a burst of inflamma-

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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tory cytokine molecules that causes the human body to attack its own cells and tissues, leading to a variety of adverse health problems (Dhama et al., 2020, Fenizia et al., 2020, Narang et al., 2020, Soy et al., 2020). SARS-CoV-2 infection led to an increase in COVID-19 disease severity from mild to severe in pregnant women and intermittent death, depending on the extent of cellular and tissue damage caused by the cytokine storm (Chaubey et al., 2021). Considering the particulars of immune status and physiological features in pregnant women, there is a need to investigate the differences in the clinical characteristics and severity of COVID-19 between pregnant and nonpregnant women and the potential impact of SARS-CoV-2 infection on the clinical outcomes of the fetus and neonate.

SARS-CoV-2 infection has been reported to be more severe in pregnant women than in nonpregnant women (Villar et al., 2021). Studies conducted in the United States and France have shown that pregnancy is a risk factor for severe disease and that COVID-19 during pregnancy may increase the risk of preterm birth, but the mortality rate among pregnant women is similar to that of nonpregnant women of the same age (Ellington et al., 2020, Kayem et al., 2020). In contrast, some studies from China showed that the clinical manifestations and characteristics of COVID-19 in pregnant women were similar to those of nonpregnant women (Cheng et al., 2020, Wei et al., 2020, Xu et al., 2020, Yu et al., 2020). In spite of the growing number of studies on pregnant women with COVID-19 worldwide, it is still unclear whether the disease severity and death rate in reproductive-aged women with SARS-CoV-2 infection vary according to pregnancy status (Godoi et al., 2021).

In Japan, the first laboratory-confirmed COVID-19 case was detected on January 16, 2020. Subsequently, the first laboratory-confirmed COVID-19 case in Osaka Prefecture was detected on January 29, 2020. As of September 30, 2021, a total of 1,696,936 patients with laboratory-confirmed COVID-19 were identified nationwide and a total of 199,553 patients were identified in Osaka Prefecture (Ministry of Health, 2021a). However, few studies have described how the COVID-19 pandemic affected reproductive-aged women in Japan, specifically comparing pregnant and nonpregnant women (Katayama et al., 2021, Tanaka et al., 2021, Zha et al., 2021). To address this knowledge gap, we conducted a retrospective observational study of reproductive-aged pregnant and nonpregnant women with COVID-19 in Osaka, Japan.

Methods

Study design and setting

We conducted a retrospective observational study on COVID-19 among reproductive-aged women in the Osaka Prefecture, Japan, between January 2020 and November 2020. The details of the data collection are described elsewhere (Hirayama et al., 2021, Zha et al., 2021). In accordance with the Infectious Diseases Control Law, the Osaka Prefecture Government conducted an active epidemiological investigation to collect epidemiological data on patients with COVID-19 using a uniform data-collection system (Government, 2020b, Ministry of Health, 2021b). Among patients with COVID-19 who were registered in the system by the end of November 2020 and whose follow-up was completed, we focused on women of reproductive age who were pregnant or not. Therefore, not all the cases in November 2020 were included.

Information on patients with COVID-19 was collected, including sex, age group, city of residence, presence of comorbidities, disease severity at diagnosis, date of symptom onset, surge, cluster, close contacts, hospital admission, date of hospital admission, date of discharge, status at discharge (alive or death), date of death, and treatment (including oxygen therapy, mechanical ventilation, renal

replacement therapy, intensive care unit [ICU] admission, and extracorporeal membrane oxygenation). Age was classified in 10-year intervals as the Osaka Prefecture Government withheld precise age information in order to protect the privacy of patients with COVID-19. Accordingly, we designated reproductive-aged women as those aged 10–49 years old in this study. The period until June 13, 2020 was considered to be the first surge, followed by the second surge between June 14 and October 9, 2020, and the third surge thereafter (Government, 2020a). A cluster was defined as a group of five or more individuals who tested positive for SARS-CoV-2 and had an epidemiological relationship to the index patient (Diseases, 2021). The local public health centers defined close contacts as those who examined, nursed, or cared for the patient without protective equipment; lived with or had prolonged contact with the patient; had contact with the patient without protection for longer than 15 minutes at a distance of less than 1 meter; or was directly exposed to contaminated materials (Diseases, 2021). Disease severity at diagnosis were categorized as mild, moderate, or severe (Ministry of Health, 2021b). The date of symptom onset was defined as the date on which the first symptoms were reported (Takeuchi et al., 2020a, Takeuchi et al., 2020b). In cases where the date of symptom onset was unknown, we used the date of medical treatment, hospital admission, or any change in symptoms, whichever occurred first.

This study was approved by the Osaka University Hospital Ethical Review Committee (reference no. 20397). The informed consent requirement was waived.

Statistical analysis

Categorical variables were reported as frequencies and proportions, and continuous variables were reported as the median and interquartile range (IQR). Pearson chi-square test was used to compare categorical variables, and the Wilcoxon rank-sum test was used to compare continuous variables between pregnant and nonpregnant women. All tests were two-tailed, and statistical significance was defined as a *P* value of < 0.05. Statistical analyses were performed using Stata version 16 (StataCorp. 2015, College Station, TX, USA).

Results

Eligible patients

Of the 14,864 patients with COVID-19, 4156 (28.0%) were reproductive-aged female patients, of whom 29 (0.7%) were pregnant and 4127 (99.3%) were nonpregnant (Figure 1).

Patient epidemiological characteristics

Table 1 shows the baseline epidemiological characteristics of the reproductive-aged female patients with COVID-19. Approximately half of the nonpregnant women (47.7%) and pregnant women (48.3%) were aged 20–29 years old. The age distribution differed significantly according to pregnancy status (*p* = 0.035). The prevalence of comorbidities was similar among pregnant and nonpregnant women (6.9% and 8.7%, respectively). The most common disease severity at the time of diagnosis was mild (3564 cases, 85.8%), followed by asymptomatic (448 cases, 10.8%). No moderate or severe cases were observed in the pregnant women, whereas 0.1% of nonpregnant patients had severe disease at the time of diagnosis. No clusters were seen among pregnant women, while 4.2% of nonpregnant women were part of a cluster. More than half of the pregnant women were considered close contacts (17 cases, 58.6%), compared with approximately one-third in the

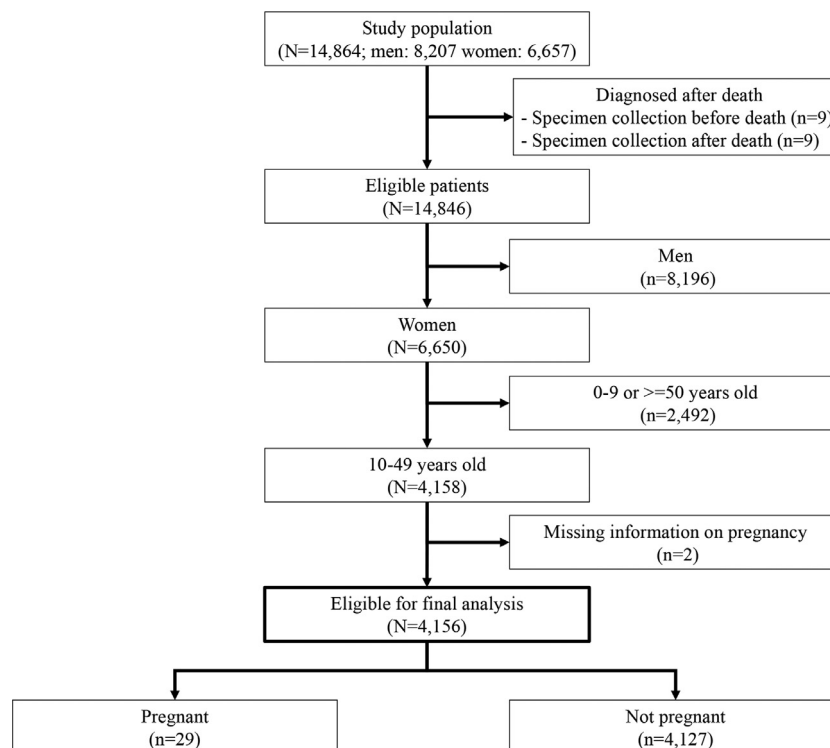


Figure 1. Patient flowchart

Legend: Of the 14,864 patients with COVID-19, 4156 (28.0%) were reproductive-aged female patients, of whom 29 (0.7%) were pregnant and 4127 (99.3%) were nonpregnant.

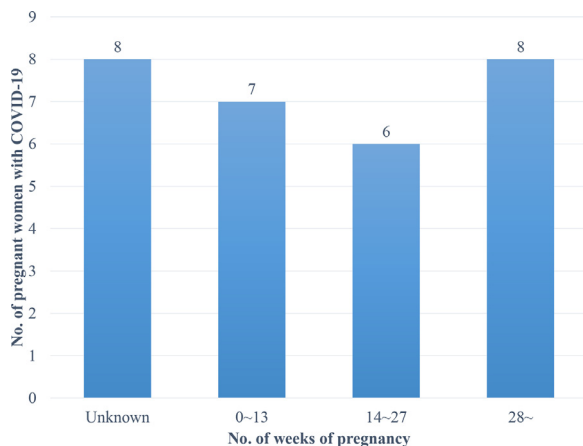


Figure 2. Distribution of gestational weeks among pregnant women with COVID-19

Legend: Figure 2 shows the distribution of gestational weeks among pregnant women with COVID-19. The number of pregnant patients were evenly distributed in the first, second, and third trimesters of gestation. The median gestation was 19 weeks among those with a known gestation.

nonpregnant group (1344 cases, 32.6%; $p = 0.003$). Of the 29 pregnant women, 22 (75.9%) were hospitalized; whereas among the nonpregnant women, 579 (14.0%) were hospitalized ($p < 0.001$).

Figure 2 shows the distribution of gestational weeks among pregnant women with COVID-19. The number of pregnant patients were evenly distributed in the first, second, and third trimesters of gestation. The median gestation was 19 weeks among those with a known gestation.

Clinical features

Table 2 shows the clinical characteristics of the hospitalized reproductive-aged female patients. The median number of days

from onset to hospitalization was 6 days (IQR: 4–9 days) in total. The median length of hospital stay was 9 days (IQR: 7–14 days) in total. The time from onset to hospitalization and the length of hospital stay did not differ significantly according to pregnancy status. One patient received oxygen therapy, but none received mechanical ventilation, renal replacement therapy, or extracorporeal membrane oxygenation, and there were no ICU admissions or deaths in pregnant women. No severe diseases or deaths were observed despite pregnancy status.

Discussion

This is a population-based retrospective study to report the characteristics and outcomes of COVID-19 among reproductive-aged female patients in Osaka Prefecture, Japan. The proportion of pregnant women with COVID-19 was < 1%. Most reproductive-aged female patients exhibited mild symptoms, and the proportion of asymptomatic patients was approximately one-tenth of the total patients. No moderate or severe cases were observed in pregnant women, while only 0.1% of severe cases were seen in nonpregnant women at diagnosis. No clusters were observed in pregnant patients; however, most of them acquired infection from a family member. Although approximately three-quarters of the pregnant women were hospitalized, only a few of the patients were hospitalized in the nonpregnant group. Moreover, no ICU admissions or deaths were observed in reproductive-aged female patients. This study provides information on the actual situation of SARS-CoV-2 infection among reproductive-aged female patients. This information could be used to help prevent its transmission.

The majority of pregnant women in this study were 30–39 years old, which is reflective of the average age of pregnant women in Japan (over 30 years old) (Statistics Bureau, 2019). Regarding the transmission route, there were no clusters among pregnant women with COVID-19. This may be because pregnant women generally follow the government recommendations to stay alert

Table 1
Epidemiological characteristics of reproductive-aged pregnant and nonpregnant women in Osaka Prefecture, Japan

Factor	Total N	(%)	Pregnant N	(%)	Not pregnant N	(%)	P-value*
No. of patients	4,156	(100.0)	29	(100.0)	4,127	(100.0)	
Age							0.035
10–19 years old	399	(9.6)	1	(3.4)	398	(9.6)	
20–29 years old	1,982	(47.7)	14	(48.3)	1968	(47.7)	
30–39 years old	923	(22.2)	12	(41.4)	911	(22.1)	
40–49 years old	852	(20.5)	2	(6.9)	850	(20.6)	
Geographic area							0.061
Osaka City	2,375	(57.1)	10	(34.5)	2365	(57.3)	
Other areas in Osaka Prefecture	1,709	(41.1)	19	(65.5)	1690	(40.9)	
Outside Osaka Prefecture	65	(1.6)	0	(0.0)	65	(1.6)	
Unknown	7	(0.2)	0	(0.0)	7	(0.2)	
Comorbidities							0.738
No	3,797	(91.4)	27	(93.1)	3770	(91.3)	
Yes	359	(8.6)	2	(6.9)	357	(8.7)	
Disease severity at diagnosis							0.899
Asymptomatic	448	(10.8)	3	(10.3)	445	(10.8)	
Mild	3,564	(85.8)	26	(89.7)	3538	(85.7)	
Moderate	3	(0.1)	0	(0.0)	3	(0.1)	
Severe	3	(0.1)	0	(0.0)	3	(0.1)	
Unknown	138	(3.3)	0	(0.0)	138	(3.3)	
Surge							0.001
First (~ Jun. 13)	465	(11.2)	9	(31.0)	456	(11.0)	
Second (Jun. 14 ~ Oct. 9)	2,629	(63.3)	18	(62.1)	2611	(63.3)	
Third (Oct. 10 ~)	1,062	(25.6)	2	(6.9)	1060	(25.7)	
Cluster							0.938
No	3,983	(95.8)	29	(100.0)	3954	(95.8)	
Medical institution	77	(1.9)	0	(0.0)	77	(1.9)	
University	9	(0.2)	0	(0.0)	9	(0.2)	
School	7	(0.2)	0	(0.0)	7	(0.2)	
Child facility	10	(0.2)	0	(0.0)	10	(0.2)	
Other clusters	70	(1.7)	0	(0.0)	70	(1.7)	
Close contact							0.003
No	2,795	(67.3)	12	(41.4)	2783	(67.4)	
Yes	1,361	(32.7)	17	(58.6)	1344	(32.6)	
Hospitalization							<0.001
No	3,497	(84.1)	7	(24.1)	3490	(84.6)	
Yes	601	(14.5)	22	(75.9)	579	(14.0)	
Unknown	58	(1.4)	0	(0.0)	58	(1.4)	

* Groups compared using Pearson chi-square test.

Table 2
Clinical characteristics of hospitalized reproductive-aged pregnant and nonpregnant women in Osaka Prefecture, Japan

Factor	Total	Pregnant	Not pregnant	P-value
No. of hospitalized patients	601	22	579	
Days to hospitalization, median (IQR) [‡]	6 (4, 9)	5 (3, 8)	6 (4, 9)	0.130*
Length of hospital stay, median (IQR) [‡]	9 (7, 14)	9 (7, 13)	9 (7, 14)	0.845*
Oxygen therapy, n (%)	23 (3.8)	1 (4.6)	22 (3.8)	0.858 [†]
Mechanical ventilator, n (%) [§]	3 (0.5)	0 (0.0)	3 (0.5)	NA
Intensive care unit, n (%)	3 (0.5)	0 (0.0)	3 (0.5)	NA
Renal replacement therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Extracorporeal membrane oxygenation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA

Abbreviations: IQR, interquartile range; NA, not available.

* Groups compared using Wilcoxon rank-sum test.

[†] Groups compared using Pearson chi-square test.[‡] Number of individuals with missing data on the following variables: days to hospitalization n = 3; length of hospital stay n = 13.[§] Mechanical ventilator including noninvasive positive pressure ventilation.

and safe and avoid going out unnecessarily during the COVID-19 pandemic in Japan. Conversely, the proportion of pregnant patients who acquired the infection from a close contact was approximately 1.5 times higher than that in nonpregnant women. As pregnant women are more likely to stay at home, the most likely source of infection among pregnant women is a family member. Therefore, to protect pregnant women from infection, in addition to self-prevention, measures should also be taken to prevent infection in their families.

The high proportion of hospitalization in pregnant patients indicates that, considering the specific situation in pregnant women,

most pregnant patients were admitted to the hospital for observation in Osaka, Japan. In this study, none of pregnant women with COVID-19 required intensive care admission or ventilatory support. Previous studies on hospitalized pregnant women with COVID-19 have shown that the proportion of cases requiring mechanical ventilator or ICU care was 1.5% to 7.6% (Elshafeey et al., 2020, Salem et al., 2021). Furthermore, no deaths were observed among the reproductive-aged female patients in this study. This result is similar to that in studies from China, which reported death rates of 0–1.5% in pregnant women with COVID-19 (Cheng et al., 2020, Wei et al., 2020, Xu et al., 2020, Yu et al., 2020). Further

observational studies are required to determine whether there are regional differences in the severity of COVID-19 and mortality rates among pregnant women with COVID-19. Understanding of the effect of SARS-CoV-2 infection, particularly its effect on pregnant women and neonates, is still insufficient. Further research is required to provide an evidence-based foundation for the medical management of pregnant patients with COVID-19.

Currently, the COVID-19 vaccination is being administered globally. As research institutes and pharmaceutical companies around the world are still conducting clinical trials on drugs that are expected to treat the SARS-CoV-2 infection, vaccination is a proven method of controlling the COVID-19 pandemic. Pregnant women were initially excluded from active vaccination because the safety of the vaccine had not been established. However, many pregnant women have been vaccinated in other countries, and the severity and frequency of adverse reactions are comparable with those seen by nonpregnant women, with no fatal adverse events reported in either the fetus or mother (Goncu Ayhan et al., 2021; Sukarno et al., 2022). In Japan, the three societies, including the Japan Society of Obstetrics and Gynecology, Japan Association of Obstetricians and Gynecologists, and Japan Society for Infectious Diseases in Obstetrics and Gynecology, issued a “Notice on COVID-19 Vaccination” for pregnant and nursing women, declaring that pregnant women are encouraged to have the vaccine, as are their husbands or partners (Gynecology, 2021). In the United States, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have issued comments strongly recommending that all pregnant women be vaccinated against COVID-19, both at term and after delivery, to avoid the risk of infection, severe illness, and death (SMFM, 2021). Given the scarcity of available drugs for pregnant women infected with COVID-19, strict and active infection prevention, including vaccination, is essential.

This study has some limitations. First, the dataset does not include information on delivery and fetal outcomes in pregnant women with COVID-19. Second, because this study analyzed epidemiological data collected by public health centers in accordance with the Infectious Diseases Control Law, specific information on comorbidities and medications was not available. Third, the data provided by Osaka Prefecture did not include all cases. In this context, the number of cases, treatment, and other information available on the Osaka Prefecture website are different from ours. Despite these limitations, this study provides important basic epidemiological information on COVID-19 among women of reproductive age in Osaka Prefecture.

Conclusions

We reveal the characteristics and outcomes of reproductive-aged female patients with COVID-19 using a comprehensive registry encompassing the whole Osaka Prefecture in Japan. Pregnant women accounted for 0.7% of the total cases of COVID-19 among women of reproductive age, and there were no deaths observed in pregnant or nonpregnant women. This study provides a baseline for long-term monitoring of COVID-19 among women of reproductive age in Osaka Prefecture.

Conflict of Interest

All authors declare no conflict of interest.

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Author contributions

LZ and TK conceived the study design. LZ and KT drafted the manuscript. LZ performed statistical analyses. TSo, AH, TT, TK, YK, SK, and TSh input their clinical expertise and critically revised the manuscript. All authors approved the version for publication. TK supervised the whole manuscript.

Ethical Approval

This study has been approved by the Research Ethics Committee of Osaka University (Approval No. 20397).

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