





BMJ Open Risk factors for severe disease and impact of severity on pregnant women with COVID-19: a case-control study based on data from a nationwide survey of maternity services in Japan

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ABSTRACT

Objective To identify independent risk factors for severe COVID-19 in pregnant women and to evaluate the impact of disease severity on preterm birth.

Design A case-control study based on data from a nationwide questionnaire-based survey of maternity services in Japan.

Setting A questionnaire was mailed to all 2135 delivery institutions in Japan between July and August 2021. A total of 1288 institutions responded (60% of all delivery institutions in Japan). 566 facilities reported having cared for pregnant women with COVID-19, and 722 facilities reported having had no such patients.

Participants One thousand and forty-three hospitalised and non-hospitalised pregnant women diagnosed with COVID-19 between July 2020 and 30 June 2021.

Primary and secondary outcome measures The primary outcome was progression to severe COVID-19. The secondary outcome was preterm birth due to COVID-19 infection.

Results 56 cases (5.4%) were severe, and 987 (94.6%) were non-severe. Multivariable logistic regression analysis showed that gestational age \geq 24 weeks (adjusted OR (aOR) 6.68, 95% CI 2.8 to 16.0) and maternal age \geq 32 years (aOR 2.40, 95% CI 1.3 to 4.3) were independently associated with severe cases. Using the Kaplan-Meier method, the probability of continued pregnancy at 14 days after diagnosis for severe cases was 0.57 between 24 and 31 weeks' gestation and 0.27 between 32 and 36 weeks' gestation. The probability for non-severe cases was 1.0 between 24 and 31 weeks' gestation and 0.8 between 32 and 36 weeks' gestation. Among the patients with COVID-19 in the preterm period, preterm birth due to infection was significantly more common in severe than non-severe cases (48% vs 6%, $p < 0.0001$).

Conclusions Severe COVID-19 in pregnant women was associated with gestational age \geq 24 weeks and maternal age \geq 32. The rate of preterm delivery due

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a case-control study based on data from a nationwide questionnaire-based survey of maternity services in Japan.
- ⇒ Hospitalised and non-hospitalised pregnant women across all trimesters of pregnancy diagnosed with COVID-19 were included.
- ⇒ Overall, 60% of the delivery facilities in Japan responded to the survey; while this represents a large number of facilities and patients, the limited response rate may affect the representativeness of the sample and the generalisability of the results.
- ⇒ This analysis is based on survey responses by unit directors based on clinical records; detailed information on laboratory data, clinical vital signs and treatment was not collected.
- ⇒ The effects of SARS-CoV-2 variants and vaccination history were not considered in this study.

to the infection was significantly higher in severe COVID-19 cases.

INTRODUCTION

Pregnant women with COVID-19 have a higher risk of developing more severe symptoms than non-pregnant women. Several studies have reported that pregnant women with COVID-19 have a greater increase in intensive care unit admission, invasive ventilation and hospitalisation for severe respiratory symptoms than infected non-pregnant women.¹⁻³

There are limited studies suggesting risk factors for COVID-19 severity in pregnant women, including case series and systematic reviews of pregnant women who required hospitalisation or delivery. A few studies have

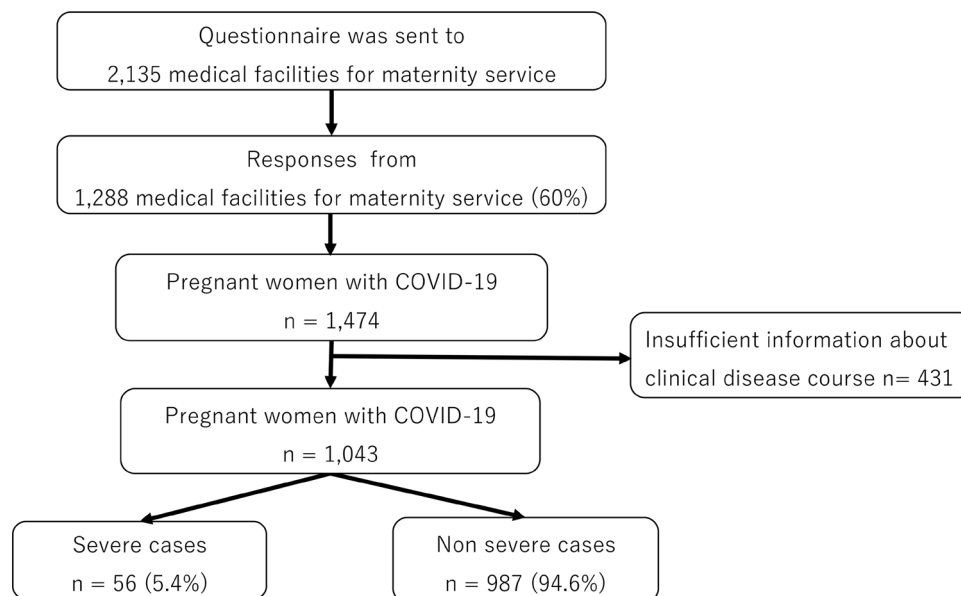


Figure 1 Study flow diagram.

examined pregnant women across all trimesters of pregnancy on a nationwide scale.^{1–6} The characteristics of pregnant women and the types of risk factors they have may vary by ethnicity and target population, which may affect the results.^{5,6} Moreover, limited information is available regarding the impact of the severity of illness and timing of infection on perinatal outcomes in pregnant women with COVID-19.^{7,8}

We have already reported the clinical characteristics of infected pregnant women from January 2020, when the first cases of COVID-19 were reported in Japan, to June 2020, when the first wave of infection ended, showing that late pregnancy may be a risk factor for exacerbation of symptoms, and familial transmission is the most common route of infection.⁹ The number of cases, including severe cases, was small, and further accumulation of cases and examination of the impact of infection on perinatal outcomes was the next issue. We investigated the risk factors of severe COVID-19 in pregnant women and the effect of severe cases on preterm birth based on the results of a nationwide questionnaire survey in Japan.

METHODS

A nationwide questionnaire-based survey examining pregnant women with COVID-19 at maternity services was conducted by the Japan Association of Obstetricians and Gynaecologists between July and August 2021. A questionnaire was mailed to the director or the chief obstetrician of fetal–maternal medicine departments of all the 2135 delivery institutions (1155 clinics and 980 hospitals) in Japan. The questionnaire consisted of a general component (online supplemental questionnaire 1) and a second, more detailed component (online supplemental materials 1 and 2). Online supplemental questionnaire 1 included questions on the number of pregnant women with COVID-19 who were diagnosed or managed within

each unit between July 2020 and June 2021. Online supplemental questionnaire 2 investigated the maternal characteristics, comorbidities, symptoms, clinical course and maternal and perinatal outcomes of both hospitalised and non-hospitalised pregnant women with COVID-19. The survey responses were received via an online platform, and all patient data were anonymised.

A confirmed case of COVID-19 was defined as having a positive real-time reverse transcriptase (RT)-PCR SARS-CoV-2 assay or antigen test for symptomatic woman from nasal and pharyngeal swab specimens, or having respiratory compromise in the presence of characteristic radiographic changes of COVID-19. During the study period, in some hospitals, SARS-CoV-2 testing was performed on patients admitted for delivery, regardless of symptoms or potential exposure to COVID-19. Nasal and pharyngeal swabs or umbilical cord blood were obtained from almost all newborns born to infected mothers, and the samples were subsequently tested using RT-PCR.

Pregnant women diagnosed with COVID-19 and for whom information on the subsequent clinical course of the infection was available were included in the study. Cases with insufficient information on the course of the infection after diagnosis were excluded. Severe COVID-19 were defined as cases with severe respiratory symptoms according to the following criteria: respiratory rate >30/min; percutaneous oxygen saturation <93% or ratio of arterial oxygen partial pressure to inspired oxygen fraction <300; and/or lung infiltrates >50% within 24–48 hours on chest imaging).¹⁰ Patients with milder than severe disease, including asymptomatic patients, were defined as non-severe cases. The primary outcome was the progression to severe COVID-19. The secondary outcome was preterm birth due to COVID-19 infection. Preterm delivery in a COVID-19-infected woman without a spontaneous onset of labour and/or with other

Table 1 Characteristics of pregnant women with COVID-19

	All patients (n=1043)		Severe cases (n=56)		Non-severe cases (n=987)		P value
	n	%	n	%	n	%	
Maternal age*							
Median (IQR) (years)	30	26–34	33	29–38	30	26–34	<0.0001
Under 20	15	1.4	0	0.0	15	1.5	1.00
20–29	471	45.2	14	25.0	457	46.4	0.002
30–39	501	48.1	34	60.7	467	47.4	0.05
Over 40	54	5.2	8	14.3	46	4.7	0.002
Characteristic							
Nulliparous†	480	46.6	22	39.3	458	47.1	0.26
Multiple pregnancy‡	17	1.7	3	5.7	14	1.5	0.06
Pregnancy period at diagnosis							
Median (IQR) (weeks)	26	16–33	32	26–35	25	15–33	<0.0001
First trimester	202	19.4	1	1.8	201	20.4	<0.0001
Second trimester	380	36.4	15	26.8	365	37.0	0.12
Third trimester	461	44.2	40	71.4	421	42.7	<0.0001
Epidemiological history							
Familial infection	537	51.5	28	50.0	509	51.6	0.82
Community acquired	164	15.7	10	17.9	154	15.6	0.65
Nosocomial infection	18	1.7	1	1.8	17	1.7	1.00
Workplace infection	50	4.8	1	1.8	49	5.0	0.51
Unknown	274	26.3	16	28.6	258	26.1	0.69
Comorbidities§							
Diabetes	8	0.8	2	3.6	6	0.6	0.07
Chronic hypertension	7	0.7	2	3.6	5	0.5	0.05
Asthma	36	3.5	4	7.1	32	3.3	0.13
Body mass index>25	37	3.6	5	8.9	32	3.3	0.045
Pregnancy complications‡							
Hypertensive disorders of pregnancy	19	1.9	2	3.8	17	1.8	0.27
HELLP syndrome	3	0.3	0	0.0	3	0.3	1.00
Gestational diabetes mellitus	40	4.0	5	9.4	35	3.7	0.06
Placental abruption	3	0.3	1	1.9	2	0.2	0.15
Deep venous thrombosis	1	0.1	0	0.0	1	0.1	1.00
Course of pregnancy							
Pregnancy ongoing	192	18.4	5	8.9	187	18.9	0.07
Delivery	526	50.4	41	73.2	485	49.1	0.001
Delivery during infection	164	15.7	28	50.0	136	13.8	<0.0001
Spontaneous abortion	12	1.2	0	0.0	12	1.2	1.00
Induced abortion	4	0.4	0	0.0	4	0.4	1.00
Stillbirth	1	0.1	0	0.0	1	0.1	1.00
Unknown	308	29.5	10	17.9	298	30.2	0.05

Data are presented as n (%) or median (IQR). The p value is a comparison of severe and non-severe cases.

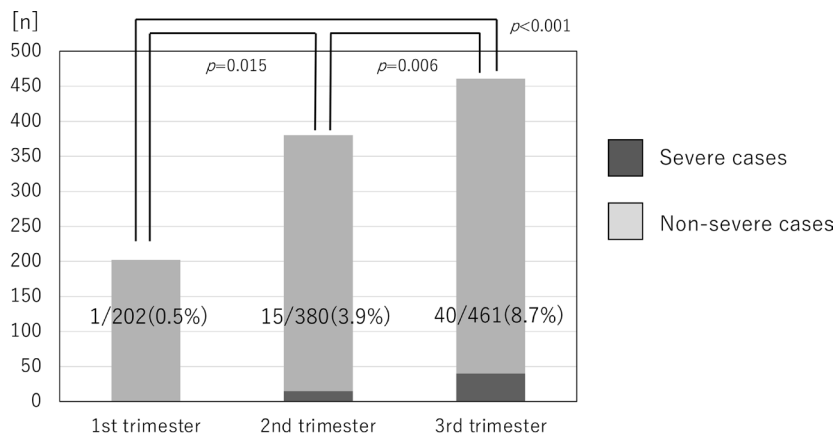
*Excluding 2 cases with missing data

†Excluding 14 cases with missing data

‡Excluding 47 cases with missing data

§Excluding 10 cases with missing data

HELLP, Hemolysis, elevated liver enzymes, and low platelet count.



The numerator represents the number of severe cases, the denominator represents the total number of COVID-19 patients, and the percentage represents the severity rate. Statistical significance in severity rates in each pregnancy periods was determined using Bonferroni correction.

Figure 2 Number of patients with COVID-19 in each trimester.

obstetrical indications was defined as preterm birth due to COVID-19 infection.

Statistical analyses

Data were analysed using JMP Pro for Mac, V.16.0.0 (SAS Institute, USA). Non-parametric continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test and Fisher's exact test. Statistical significance was defined as a P value < 0.05. In the statistics of the categorical variables for the three groups, p values were adjusted using the Bonferroni correction. Multivariate analysis was performed using logistic regression analysis. Significant variables determined by univariate analyses, including maternal age, gestational week at diagnosis, diabetes, chronic hypertension, body mass index (BMI) > 25 (as per the definition of obesity by the Japan Society for the Study of Obesity) and asthma, were used in the multivariable analysis to identify the risk factors. Using cut-off values obtained from ROC (receiver operating characteristic) curves, maternal age ≥ 32 years at diagnosis and gestational age ≥ 24 weeks were used as categorical variables. The cumulative delivery curves were compared using the log-rank test. Events were defined as delivery due to COVID-19 infection, and censoring was defined as delivery due to obstetrical indication or spontaneous delivery. Events and censoring occurring after 14 days of diagnosis were treated as occurring on day 14.

Table 2 Logistic regression analysis for severe COVID-19 in pregnant women

Variable	Adjusted OR	95% CI	P value
Maternal age ≥ 32 years	2.40	1.33 4.31	0.004
Gestational age at diagnosis ≥ 24 weeks	6.68	2.79 16.00	<0.0001
Diabetes	3.51	0.62 19.89	0.16
Chronic hypertension	5.78	0.81 41.21	0.08
Body mass index > 25	1.80	0.60 5.37	0.29
Asthma	2.53	0.83 7.73	0.10

Patient and public involvement

None.

RESULTS

The study flowchart is shown in figure 1. Questionnaires were sent to 2135 medical facilities (1155 clinics and 980 hospitals) with maternity services. Responses were received from 1288 facilities (678 clinics and 610 hospitals), with a response rate of 60.3%. A total of 722 facilities (423 clinics and 299 hospitals) reported no cases, 536 facilities (255 clinics and 281 hospitals) reported fewer than 10 cases and 30 hospitals reported more than 10 cases. Excluding 89 cases that were reported as overlapping by some facilities, 1474 pregnant women with confirmed COVID-19 were reported between July 2020 and 30 June 2021. Approximately 251 764 deliveries occurred in the afore-mentioned 1-year period in the institutions that participated in the survey. The estimated incidence rate of COVID-19 over the study period was 585.5 per 100 000 pregnant women. Of these, 431 cases were excluded from further consideration because of insufficient information on the clinical course of the infection after diagnosis. In total, 1043 hospitalised and non-hospitalised pregnant women were included in this analysis, of whom 56 (5.4%) were severe and 987 (94.6%) were non-severe cases. Non-severe cases included 214 asymptomatic patients. Overall, 60 women (5.8%) required oxygen administration and 12 (1.2%) required mechanical ventilation. There was no maternal death. Among the 164 births during the maternal infection period, no case of SARS-CoV-2 transmission to newborns was reported.

The characteristics of pregnant women with COVID-19 are shown in table 1. The median maternal age was higher in the severe than in the non-severe cases (33 vs 30 years, $p < 0.0001$). The gestational age at COVID-19 diagnosis was significantly higher in severe cases than in non-severe cases (32 vs 25 weeks, $p < 0.0001$). Regardless of severity, the most common route of infection was familial (52%). Regarding maternal comorbidities, BMI > 25 was more

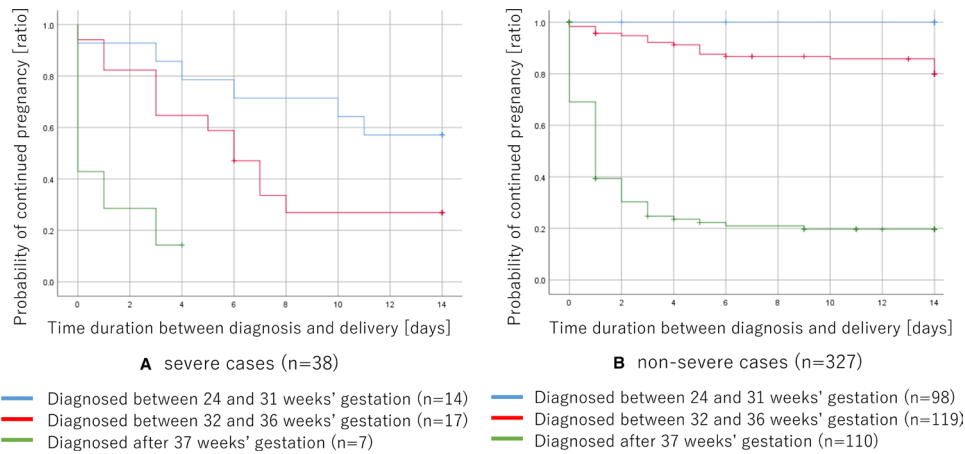


Figure 3 The cumulative delivery curves regarding the interval between the diagnosis of COVID-19 infection and the delivery due to COVID-19 infection. (A) Severe cases. (B) Non-severe cases.

common in severe cases than in non-severe cases (8.9% vs 3.3%, $p=0.045$). No differences in pregnancy complications were observed between the two groups. As shown in figure 2, the percentage of severe cases by trimester was highest in the third (8.7%) and lowest in the first trimester (0.5%).

Multivariable logistic regression analysis showed that gestational age ≥ 24 weeks (adjusted OR (aOR), 6.68; 95% CI 2.8 to 16.0) and maternal age ≥ 32 years (aOR, 2.40; 95% CI 1.3 to 4.3) were independently associated with severe cases (table 2).

Among 526 patients who delivered, the cumulative delivery curves were prepared for 365 patients who delivered after 24 weeks of gestation and for whom the clinical course of delivery was known regarding the interval between the diagnosis of COVID-19 infection and the delivery due to infection. In total, 38 severe and 327 non-severe cases are shown in figure 3A,B, respectively. Using the Kaplan-Meier method, the probability of continued pregnancy at 14 days after diagnosis for severe cases was 0.57 between 24 and 31 weeks' gestation and 0.27 between 32 and 36 weeks' gestation. The probability for non-severe cases was 1.0 between 24 and 31 weeks' gestation and 0.80 between 32 and 36 weeks' gestation. This probability was significantly different between the two groups by the log-rank test ($p < 0.0001$ for both preterm periods). No difference in this probability among those diagnosed after 37 weeks of gestation was noted in both groups ($p=0.36$). Among the COVID-19 cases diagnosed during the entire preterm period, preterm birth due to infection was found in 48.4% (15/31) of the severe cases and 6.0% (13/217) of the non-severe cases; thus, significantly more in the severe cases ($p < 0.0001$).

DISCUSSION

The current nationwide survey revealed that gestational age ≥ 24 and maternal age ≥ 32 years were independently associated with severe COVID-19 in pregnant women. In severe cases, the rate of preterm delivery due to infection was significantly higher than in non-severe cases.

Previous systematic reviews and meta-analyses had also reported older maternal age as a risk factor. However, gestational age at the time of infection had not been associated with illness severity.¹⁴⁶ These studies have not fully examined the association between each trimester and the severity of illness, including the lack of data on the gestational age at symptom onset and the fact that most enrolled cases were in the third trimester. Differences in ethnicity and target population may also have had an impact. Our results show a similar trend to other studies that reported the second and third trimesters of pregnancy as risk factors for moderate and severe COVID-19 in pregnant women.⁵ Our study examined a larger number of cases by subdividing the severity of the disease and found that severe cases were associated with late pregnancy (ie, the second half of the second trimester and later). Other reports of more cases requiring hospitalisation or severe cases in late pregnancy may support our results.⁷⁹¹¹ The higher risk of severe illness in late pregnancy is similar to that of other respiratory viral infections, such as influenza.¹²¹³ Increased oxygen consumption, compromised cardio-pulmonary function due to diaphragm displacement and reduced functional residual capacity during pregnancy may become more pronounced in advanced pregnancy periods.² These maternal physiological adaptations of the cardiovascular and respiratory systems and immunological changes during pregnancy may result in reduced tolerance to respiratory infections and pneumonia, especially in the later pregnancy period.¹⁴ Maternal pre-existing conditions noted in other reports¹⁴⁶ were not associated with severity in this report. The low incidence of maternal comorbidities may have influenced our results. Symptoms such as shortness of breath and elevated lactate dehydrogenase levels have also been reported as risk factors for severe disease.¹⁵ These factors require further study.

The probability of continuing pregnancy at 14 days after COVID-19 diagnosis in severe cases was 0.57 in the extremely and very preterm period and 0.27 in the moderate and late preterm periods, significantly lower than that in non-severe cases, due to preterm delivery

with infection as an indication. During this period in Japan, because the disease was considered infectious within 14 days of diagnosis, we examined the cumulative delivery curves for infection within the first 14 days of diagnosis. As a whole, 48% of severe cases resulted in preterm delivery due to infection, compared with 6% of non-severe cases. While some papers have reported on the severity and timing of delivery,^{7,8} these reports are limited in that they include both term and preterm cases, and it is unclear whether the indication for delivery is infectious or obstetrical. Therefore, we focused on cases of infection control, distinguished the timing of infection, clarified the reasons for preterm delivery and analysed the delivery timing.

Pregnant women with COVID-19 who are at risk for severe disease should be managed with the expectation of treating not only critically ill mothers but also preterm infants. For hospitalised patients at risk, information sharing with advanced medical facilities is necessary, and careful follow-up is needed for non-hospitalised patients at risk. In addition, pregnant women who are at risk for severe disease, their families and any cohabitants should take good infection control measures and consider vaccination.^{16,17}

In the present results, the disease severity did not affect the incidence of pregnancy complications, spontaneous abortion and stillbirth. Early gestational age at infection and maternal ventilatory support have been reported to be related to adverse fetal outcomes.¹⁸ Our study did not examine the effect of COVID-19 infection severity on the fetus. Pregnant women with COVID-19 have been reported to have higher anxiety levels due to concerns about negative effects on their newborns.¹⁹ It has been shown that fetal growth, cardiac function and cerebral growth are not affected by maternal infection.^{20–22} However, there are few studies on the effects of maternal COVID-19 infection severity on the fetus, and further investigation is needed.

Strengths and limitations

A major strength of this study is that it is a large nationwide survey that included both hospitalised and non-hospitalised patients across all trimesters of pregnancy. The other important aspect of the study is that it examined the effect of disease severity on preterm delivery, focusing on the cases during the infection and identifying the reasons for delivery.

This study had the following limitations. Since this was a survey based on a questionnaire and the response rate was 60%, there is a possibility of sampling bias. Although the percentages of clinics and hospitals among the facilities that answered the questionnaire (53% and 47%, respectively) matched the ratio of clinics to hospitals among all delivery institutions in Japan (54% and 46%, respectively), the potential risk of non-response bias cannot be excluded, which may affect the representativeness of the sample and the generalisability of the results. Second, this analysis was based on a retrospective questionnaire

reporting the clinical condition of COVID-19 infection, and it did not collect detailed information on laboratory data, clinical vital signs, treatment, maternal comorbidities and epidemiological history. These survey responses depended on the judgement of each responding physician based on the medical record, and uncertainty cannot be completely eliminated. Although most preterm deliveries were attributed to infection, no data were collected on the more detailed maternal conditions for which deliveries were indicated. For a more detailed examination of severe cases in particular, an analysis by a national surveillance system is desirable. Third, because little information on mutant strains of SARS-CoV-2 was available, we did not examine mutant strains. During the study period, α variants were predominant,²³ and δ and \omicron strains require further study. Lastly, detailed data on vaccination histories were also not included in the analysis. As this study was conducted before the SARS-CoV-2 vaccine was widely distributed in Japan, the majority of patients in this study were considered unvaccinated.

CONCLUSION

Severe COVID-19 in pregnant women were associated with the second half of the second trimester of pregnancy or later and with higher maternal age. In severe cases, the rate of preterm delivery due to infection was significantly higher. Pregnant women with COVID-19 at risk for severe cases should be managed in anticipation of treatment of both severely ill mothers and preterm infants.

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Contributors TA, JH, and AS conceived the study. TA, JH and AS drafted the initial protocol, analysed the data and wrote the first draft of the manuscript. All authors collected the data. TA, JH, AS and II coordinated the study. TA, JH and AS developed the database and analysed the data. All authors contributed to the drafting of the manuscript. II, TI and KK were the guarantors of this study. All authors had full access to the study data and take responsibility for the integrity of the data and accuracy of the data analysis.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study was performed as an investigation of the Japan Association of Obstetricians and Gynecologists (JAOG) and was approved by the ethics board of the JAOG (No. 82, 22 June 2021). As this was a retrospective analysis based on a questionnaire survey, all patient records and data were anonymised by the institutions prior to submission for analyses, and the ethics committee of the JAOG waived the requirement for informed consent from each subject.

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Data availability statement Data are available upon reasonable request. The anonymised patient data analysed in this study are available from the corresponding author upon reasonable request.

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