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Maternal and perinatal outcomes of SARS-CoV-2 infection in unvaccinated pregnancies during Delta and Omicron waves

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Contribution

What are the novel findings of this work?

SARS-CoV-2 infection in unvaccinated pregnant women during the Delta wave (compared with the prior wild-type and Alpha variant epochs) was associated with higher rates of maternal death and greater need for oxygen supplementation, mechanical ventilation, and extracorporeal membrane oxygenation. However, disease severity and pregnancy complications during the Omicron wave were similar to those observed during pre-Delta epoch. This finding was limited by a small sample size.

What are the clinical implications of this work?

Among unvaccinated women, infection during the Delta wave (compared with pre-Delta) was associated with worse maternal outcomes and preterm birth before 34+0 weeks' gestation. However, the severity of infection and pregnancy outcomes during the Omicron wave (compared with pre-Delta) were similar, with no evidence of milder disease associated with Omicron. To minimize the risks of COVID-19 during pregnancy, COVID-19 vaccination remains critically important.

ABSTRACT

Objectives: Currently, there is little evidence related to the effects of the Omicron variant on pregnancy outcomes, particularly in unvaccinated women. This study aims to compare pregnancy outcomes of SARS-CoV-2 infected, unvaccinated women during the pre-Delta, Delta, and Omicron waves.

Methods: This was a retrospective cohort study at two tertiary care facilities: Sancaktepe Training and Research Hospital, Istanbul, Turkey, and St. George's University Hospitals NHS Foundation Trust, London, UK. Included were people testing RT-PCR positive for SARS-CoV-2 during pregnancy, between April 01, 2020 and February 14, 2022, and divided into three epochs: (i) **pre-Delta**, 1 Apr 2020 to 8 Jun 2021 in Turkey, and 1 Apr 2020 to 31 Jul 2021 in the UK; (ii) **Delta**, 9 Jun 2021 to 27 Dec 2021 in Turkey, and 1 Aug 2021 to 27 Dec 2021 in the UK; and (iii) **Omicron**, after 27 Dec 2021 in each of Turkey and the UK, according to the date of their positive RT-PCR test. Baseline data collected included maternal age, parity, body mass index (BMI), smoking status, gestational age at diagnosis, and comorbidities. The primary outcome was the need for oxygen supplementation, classified as oxygen support via nasal cannula or breather mask, non-invasive mechanical ventilation with continuous positive airway pressure (CPAP) or high-flow oxygen, mechanical ventilation with intubation, or extracorporeal membrane oxygenation (ECMO). Inferences were made after balancing of confounders, using an evolutionary search algorithm.

Results: 1285 RT-PCR-proven SARS-CoV-2 infections of unvaccinated pregnant women were identified during the pre-Delta (N=870), Delta (N=339), and Omicron (N=77) epochs. In the confounder-balanced cohort, infection during the Delta wave was associated with increased need for nasal oxygen support (RR 2.53, 95% confidence interval [CI] 1.75-3.65, P<.001), CPAP or high-flow oxygen (RR 2.50, 95% CI 1.37-4.56, P=.002), mechanical ventilation (RR 4.20, 95% CI 1.60-11.0, P=.003), and ECMO (RR 11.0, 95% CI 1.43-84.7, P=.021). The maternal mortality rate was also 3-4 fold higher during the Delta wave compared to pre-Delta (5.3% vs 1.5%, P=0.010).

An infection during the Omicron wave was not associated with an increased need for nasal oxygen support (RR 0.62, 95% CI 0.25-1.55, P=0.251), CPAP or high-flow oxygen (RR 1.07, 95% CI 0.36-3.12, P=0.906), or mechanical ventilation (RR 0.44, 95% CI 0.06-3.45, P=0.438). The maternal mortality rate was similar during the Omicron wave and the pre-Delta period (1.3% vs 1.3%, P=0.999). Nasal oxygen support during the Omicron wave was significantly lower compared to Delta-wave infection (RR 0.26, 95% CI 0.11-0.64, P=0.003). Perinatal outcomes were available for a subset of the confounder-balanced cohort. Preterm birth below

34 weeks' gestation was significantly increased (P<0.001) during the Delta wave compared with pre-Delta.

Conclusions: Among unvaccinated pregnant women, SARS-CoV-2 infection during (vs. before) the Delta wave was associated with increased requirement for oxygen support (including ECMO) and higher maternal mortality. Disease severity and pregnancy complications were similar during the Omicron wave (vs. pre-Delta). SARS-CoV-2 infection in unvaccinated pregnant women carries considerable risks of morbidity and mortality, and COVID-19 vaccination remains key. Miscommunication of risks of Omicron infection may adversely impact the vaccination rate among pregnant women, who are already at increased risk of complications related to COVID-19.

INTRODUCTION

During the COVID-19 pandemic, there have been several peaks of infection, caused primarily by SARS-CoV-2 variants of concern (VOC), labelled alphabetically in chronological order. The first few pandemic peaks were caused by the wild-type and Alpha variant (B.1.1.7), against which available vaccines render strong immunity. The Delta variant (B.1.617) was more virulent than Alpha, and demonstrated some immune escape from vaccines, making them somewhat less effective [1]. The more recent Omicron variant (B.1.1.529) has shown even greater immune escape, leading to record case numbers (but not increased mortality) in every country where it was detected [2 3]. This has been widely interpreted to mean that the Omicron variant is less virulent; however, health authorities have advised caution, as data on Omicron infection have been derived largely from countries with high vaccination rates [4].

COVID-19 disease is associated with excess maternal and perinatal mortality and morbidity [5]. Some evidence suggests that the Delta variant (compared with the wild-type strain and Alpha variant) causes more severe disease in pregnancy and a heightened risk of stillbirth [6]. However, there is little evidence related to the effect of the Omicron variant on pregnancy outcomes, particularly in unvaccinated women. This study aims to compare pregnancy outcomes of SARS-CoV-2 infected, unvaccinated women during the pre-Delta, Delta, and Omicron epochs.

METHODS

This was a retrospective cohort study at two tertiary care facilities: Sancaktepe Training and Research Hospital, Istanbul, Turkey, and St. George's University Hospitals NHS Foundation Trust, London, UK. Included were COVID-19 unvaccinated women, who tested RT-PCR positive for SARS-CoV-2 during pregnancy, between April 01, 2020 and February 14, 2022. The study cohort was divided into three epochs according to the date of their positive RT-PCR test and official resources delineating the periods of dominance of the Delta and Omicron VOC in each country[7]: (i) **pre-Delta**, as 1 Apr 2020 to 8 Jun 2021 in Turkey, and 1 Apr 2020 to 31 Jul 2021 in the UK; (ii) **Delta**, as 9 Jun 2021 to 27 Dec 2021 in Turkey, and 1 Aug 2021 to 27 Dec 2021 in the UK; and (iii) **Omicron**, after 27 Dec 2021 in each of Turkey and the UK.

Testing indications for SARS-CoV-2 included admission for obstetric indication (e.g., birth episode), COVID-19 symptomatology, and exposure to someone with confirmed SARS-CoV-2 infection. The management of infected women was similar in both centers. Oxygen supplementation with nasal cannula was started for women with oxygen saturation below 95%, severe shortness of breath, or tachypnea. When target oxygen saturation was not maintained on standard flow, the level of oxygen support was escalated to breather mask with reservoir and high-flow oxygen. Women who required high-flow oxygen support to maintain a target oxygen saturation were started on steroid treatment. Non-invasive mechanical ventilation with continuous positive airway pressure (CPAP), mechanical ventilation with intubation, and extracorporeal membrane oxygenation (ECMO) were utilized in sequential manner in women failing to maintain target oxygen saturation levels. Processes of care that were not included as outcomes were maternal intensive care unit (ICU) admission, and therapies such as convalescent plasma, remdesivir, and interleukin inhibitors; indications for their use varied between the study centers and during different stages of the pandemic.

Study data were collected from electronic records, and included baseline characteristics (such as maternal age, parity, body mass index [BMI], smoking status, gestational age at diagnosis and comorbidities), maternal complications, and perinatal outcomes. The main outcome measure was the need for respiratory support, with levels classified as oxygen support via nasal cannula or breather mask, CPAP or high-flow oxygen, or mechanical ventilation with intubation or ECMO.

Statistical Analysis

Baseline characteristics and outcomes were compared using Chi-squared, Fisher's exact test, t-test, or Mann-Whitney-U test, as appropriate. Confounders were selected from the published literature. Exposure groups (pre-Delta vs. Delta and pre-Delta vs. Omicron) were matched for confounders using propensity score matching with an evolutionary search algorithm. Selected confounders were maternal age, body-mass index and gestational age at diagnosis [8]. The confounders were investigated and chosen among a set of candidate variables (maternal age, body-mass index, parity, gestational age at diagnosis, comorbidities) in a previous study based on a similar cohort [8]. Balance was optimized for the confounders and the balance checks were performed using propensity score histograms and randomization checks for Mahalanobis distance. Standardized mean differences in baseline characteristics between the groups were calculated with the aim of reducing differences below 10%. Matching ratio was selected with the aim of minimizing discarded subjects (i.e., unmatched individuals) and reaching optimal confounder balance.

Sensitivity analyses were performed with smaller and larger matching ratios, to check the robustness of estimates. Also, after matching, the effects were estimated using generalized estimating equations, thereby avoiding potential bias from exclusion of cases for which confounder-matching could not be achieved; match identifiers were treated as random-effects, while variant wave and other predictor variables were treated as fixed-effects. Stability of estimates were tested with generalized linear-mixed effects models using both match identifiers and treatment centers as random-effects but these set of results were not reported if both analyses had similar results.

Effect estimates were reported as risk ratios and 95% confidence intervals (CI). All analyses were performed using R for Statistical Computing Software (Vienna, Austria) and P values less than 0.05 were considered statistically significant.

RESULTS

During the inclusion period, 1285 unvaccinated pregnant women with RT-PCR-proven SARS-CoV-2 infection were identified, during the pre-Delta (N=870), Delta (N=339), and Omicron (N=77) epochs. Majority of the cases were from Turkey (n=1159) and the remainder from UK (n=126).

Among our study population, the rates of mechanical ventilation (invasive or non-invasive) were 6.2% pre-Delta, 14.7% during the Delta wave, and 4.7% during the Omicron wave. The bimonthly average proportion of positive cases requiring mechanical ventilation reached a peak towards the second half of the Delta wave (22.1%), followed by a precipitous drop during the Omicron wave (to 4.7%) (Figure 1).

Pre-Delta period vs Delta wave infections

Table 1 shows that pregnant women infected with SARS-CoV-2 during (vs. before) the Delta wave were slightly older, with higher BMI, and later gestational age at diagnosis (including diagnosis in the third trimester), all factors known to increase the risk of severe COVID-19. After 1:1 matching for baseline characteristics, the confounder-balanced cohort showed standardized mean differences in baseline factors that were small and within 10% (Table 1, Figure S1a).

Table 2 shows that in the confounder-balanced cohort, SARS-CoV-2 infection during the Delta (vs. pre-Delta) wave was associated with an increased need for oxygen supplementation, defined by heightened need for nasal oxygen support, CPAP or high-flow oxygen, mechanical ventilation, and ECMO. In addition, in the Delta (vs. pre-Delta) epoch, maternal death was 3-4 fold higher (5.3% vs. 1.5%, P=0.010) and very preterm birth (prior to 34+0 weeks' gestation) significantly increased (15.4% vs. 4.9%, P<0.001). The rates of preeclampsia, preterm birth before 37+0 weeks' gestation, and stillbirth did not differ between Delta and pre-Delta epochs, although absolute rates were higher in the Delta-dominant period.

Pre-Delta period vs Omicron wave infections

Table 3 shows that pregnant women infected during the Omicron wave (vs. pre-Delta period) were heavier, and acquired their infection at a much later gestational age. As such, women infected during the Delta wave (vs. pre-Delta) had a much higher baseline risk of severe COVID-19. A 4:1 match of pre-Delta and Omicron wave infection cases was needed for adequate balancing in the confounder-balanced cohort, achieving standardized mean differences in baseline characteristics between the groups within 10% (Table 3, Figure S1b).

Table 4 shows that in the confounder-balanced cohort, infection during the Omicron wave (vs. pre-Delta epoch) was associated with a similar need for oxygen supplementation, however defined, and there were no differences in maternal death or preeclampsia. Also, for the subset of the cohort for which delivery outcomes were available, there were no differences in preterm birth or stillbirth during the Omicron wave (vs. the pre-Delta epoch). The 95% CI are wide, and include important potential harms and benefits associated with Omicron (vs. pre-Delta) epochs.

Omicron period vs Delta wave infections

Table S1 shows that in the confounder-balanced cohort, infection during the Omicron wave (vs. Delta epoch) was associated with a 74% reduced risk of nasal oxygen support (24.7% vs. 6.5%). While, invasive respiratory support (4.5 vs 1.3%, Delta vs. Omicron, respectively) and maternal death (3.2 vs. 1.3%) was lower in the Omicron (vs. Delta) epoch, differences did not reach statistical significance.

Sensitivity analyses

Without excluding any data, and adjusting for any effects of confounders via multiple log-binomial regression, our results agreed with the previous analysis that infection during the Delta wave was associated with a significantly greater need for advanced respiratory support (invasive or non-invasive mechanical ventilation; adjusted RR 2.19, 95% CI 1.44-3.35, P<0.001), while no significant difference was observed during the Omicron (vs. pre-Delta) epoch (adjusted RR 0.78, 95% CI 0.23-1.95, P=0.644) (Table 5). The factors associated with requirement for advanced respiratory support (non-invasive or invasive mechanical ventilation) using generalized estimating equations with log-binomial link function using treatment centers as clusters are shown in Table 5.

DISCUSSION

Summary of the key study findings

Among unvaccinated pregnant women, SARS-CoV-2 infection during the Delta wave (vs. pre-Delta) was associated with increased requirement for oxygen support (including ECMO) and higher maternal mortality. Conversely, infection severity and complications during the Omicron wave were similar, and not significantly milder, compared with the pre-Delta period. Our findings were consistent among confounder-matched cohort estimates and multiple regression-adjusted estimates. While we cannot rule out smaller effects for a milder disease course during the Omicron wave, SARS-CoV-2 infection in unvaccinated pregnant women still carried considerable risks for both morbidity and mortality.

Strengths and limitations

The main strengths of this study are, first, that it provides data related to maternal and perinatal outcomes associated with SARS-CoV-2 infection during the Delta and Omicron waves. Study centers in two countries were similar in terms of size, delivery capacity and stringency of governmental restrictions during the course of the pandemic. Second, we investigated maternal and perinatal outcomes in three time periods, to compare between the Omicron, Delta, and pre-Delta variants. However, variant sequencing data were unavailable, and a proxy (i.e. time of infection) was used to indicate the predominant variant. Of note, data related to previous SARS-CoV-2 infection were not ascertained, taking into account that the majority of cases could be asymptomatic. Moreover, perinatal outcomes such as preterm birth and stillbirth are susceptible to time-varying confounding and the observed effects are likely overestimated. Collider bias is a common issue in COVID-19 literature and testing indications may have influenced our findings. Inclusion of asymptomatic individuals who were tested as per admission protocol may have affected the estimates. However, true asymptomatic rate is likely to be underestimated in the sample and we may have overestimated the severity of Omicron infection in our cohort. Omicron-wave cohort was small and estimates smaller than a ~3-fold change would not be statistically significant hence we cannot rule-out the possibility of a milder course with Omicron. Finally, the severity of the disease may be confounded by the availability of antiviral treatment during the period when Omicron was the dominant variant, resulting in milder COVID-19.

Interpretation of study findings and comparison with published literature

In our study, we observed a more severe clinical course in infected pregnant women during the Delta wave, and maternal mortality was increased. These findings are consistent with the

limited literature on SARS-CoV-2 VOCs and greater severity of maternal disease during the Delta wave [6,9]. All related studies have taken our approach of using the date of SARS-CoV-2 infection as a surrogate for viral variant, as genotyping each infection is not commonly available. While the absolute rate of stillbirth in our study did not reach statistical significance, the report from the Centers for Disease Control (CDC) and Prevention, United States, found that infections during the Delta wave were associated with an increased incidence of stillbirth, compared with previous waves (i.e., wild type and Alpha variant) [6]; the more severe infections during the Delta wave raises the possibility that disease severity is a mediator of stillbirth. Our findings are not consistent with widely-reported observations that the Omicron variant is associated with less severe clinical infection outside pregnancy.

Clinical and research implications

As yet, there are no data on the severity of Omicron infection in unvaccinated pregnant women compared with previous variants. A recent report from our group showed that vaccinated women infected during the Omicron wave had neither moderate nor severe disease, while unvaccinated pregnant women were more likely to need oxygen support [10]. This emphasizes the importance of vaccination to pregnant women, even during the Omicron wave, during which the efficacy of vaccination against SARS-CoV-2 infection is diminished. Vaccination with an mRNA vaccine is safe and effective, but is still underutilized in pregnant women [11,12]. Pregnant women already have high levels of vaccine hesitancy, and miscommunication of protective effects of the vaccine or risk associated with COVID-19 could have dire consequences [11]. While there is widespread media coverage of reduced virulence of SARS-CoV-2 during the Omicron wave, our data suggest that this is not the case for unvaccinated pregnant women. This must be emphasized in public messaging. Moreover, further research is required for assessing the effectiveness of available vaccines (e.g. mRNA, viral vector) for preventing SARS-CoV-2 infection and related morbidities in pregnant women.

Conclusion

In unvaccinated pregnant women, infections during the Delta wave were more severe compared with previous waves; however, there was no clear evidence of reduced severity during the Omicron (vs. pre-Delta) wave. Miscommunication of risks may adversely influence the vaccination rate among pregnant women, who are already at increased risk of adverse maternal and perinatal events related to COVID-19.

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Figure legends

Figure 1. Total monthly number of cases and proportion requiring mechanical ventilation pre-Delta, during the Delta wave and during the Omicron wave. Dashed lines show the bimonthly average rate of cases requiring non-invasive or invasive mechanical ventilation. Pre-∆ = pre-Delta; ∆ = Delta; O-era = Omicron era.

Figure S1. Propensity score histograms and Mahalanobis distance density plot checking for complete randomization. Groups were balanced regarding propensity scores (a and b, Delta and Omicron, respectively) and randomization check using Mahalanobis distance (c and d, Delta and Omicron, respectively) showed successful matching (P=0.908 and 0.965, Delta and Omicron, respectively).

Table 1. Comparison of baseline characteristics among SARS-CoV-2 infected pregnant people before and after Delta became the predominant strain.

Variables, before matching	**Pre-delta (n=870)**	**Delta-wave (n=339)**	***P value***	***SMD***
Maternal age in (years)	29.1 ± 5.62	30.3 ± 5.45	<.001	0.218
• <25	212 (24.4)	54 (16.0)	.004	0.143
• ≥25 and <38	587 (67.5)	251 (74.0)		
• ≥38	71 (8.1)	34 (10.0)		
Maternal BMI (kg/m^2)	25.3 (23.8 – 27.9)	26.7 (24.1 – 29.0)	<.001	0.120
• <25	416 (47.8)	117 (34.5)	<.001	0.186
• 25 to <30	316 (36.3)	169 (49.9)		
• ≥30	138 (15.9)	53 (15.6)		
Gestational age at diagnosis (weeks)	27.3 ± 10.1	29.6 ± 8.54	<.0001	0.248
Multiparous	584 (67.1)	232 (68.4)	.662	0.028
Trimester at diagnosis				
• First	115 (13.2)	24 (7.1)	.0005	0.251
• Second	291 (33.5)	98 (28.9)		
• Third	464 (53.3)	217 (64.0)		
Comorbidities				
• Pre-gestational diabetes	10 (1.1)	4 (1.2)	.964	0.003
• Pulmonary disease	11 (1.3)	6 (1.8)	.502	0.041
• Chronic hypertension	10 (1.1)	5 (1.5)	.646	0.028
Variables, after matching	**Pre-delta (n=339)**	**Delta-wave (n=339)**	***P value***	***SMD***
Maternal age (years)	30.2 ± 5.35	30.3 ± 5.45	.820	0.017
• <25	55 (16.2)	54 (15.9)	.823	0.038
• ≥25 and <38	255 (75.2)	251 (74.1)		
• ≥38	29 (8.6)	34 (10.0)		
Maternal BMI (kg/m^2)	26.0 (24.0-28.3)	26.6 (24.0-29.0)	.586	-0.006
• <25	117 (34.5)	117 (34.5)	.999	0.000
• 25 to <30	169 (49.9)	169 (49.9)		
• ≥30	53 (15.6)	53 (15.6)		

Gestational age at diagnosis (years)	29.3 ± 8.7	29.6 ± 8.53	.612	0.038
Multiparous	243 (71.7)	232 (68.4)	.356	-0.070
Trimester at diagnosis				
• First	25 (7.4)	24 (7.1)	.619	0.061
• Second	109 (32.1)	98 (28.9)		
• Third	205 (60.5)	217 (64.0)		
Comorbidities				
• Pre-gestational diabetes	6 (1.8)	4 (1.2)	.524	0.062
• Pulmonary disease	2 (0.6)	6 (1.8)	.154	0.109
• Chronic hypertension	6 (1.8)	5 (1.5)	.761	-0.023

SMD: standardized mean difference, BMI: body-mass index

Data are presented as mean ± SD, median (IQR) or number (%).

Table 2. Association of SARS-CoV-2 infection during the Delta dominant wave with maternal and perinatal adverse outcomes in confounder matched cohort of pre-Delta wave infection.

Variables	**Pre-delta (n=339)**	**Delta-wave (n=339)**	**RR (95% CI)***	***P value***
Maternal adverse outcomes				
• Preeclampsia	12 (3.5)	8 (2.3)	0.66 (0.27 – 1.61)	.367
• Nasal O_2 support	34 (10.0)	86 (25.4)	2.53 (1.75 – 3.65)	<.001
• CPAP or high-flow O_2	14 (4.1)	35 (10.3)	2.50 (1.37 – 4.56)	.002
• Mechanical ventilation	5 (1.5)	21 (6.2)	4.2 (1.60 – 11.0)	.003
• ECMO	1 (0.3)	11 (3.5)	11.0 (1.43 -84.7)	.021
• Maternal death	5 (1.5)	18 (5.3)	3.60 (1.35 – 9.58)	.010
Perinatal adverse outcomes	**Pre-delta (n=308)**	**Delta-wave (n=123)**		
• Preterm birth <37 weeks	55 (17.8)	31 (25.2)	1.41 (0.96 – 2.08)	.081
• Preterm birth <34 weeks	15 (4.9)	19 (15.4)	3.17 (1.67 – 6.04)	<.001
• Stillbirth	3 (1.0)	4 (3.2)	2.10 (0.51 – 8.74)	.304

*Generalized estimating equations with log-binomial link function using matching ID as clusters

ECMO: extracorporeal membrane oxygenation, CPAP: continuous positive airway pressure, RR: risk ratio

Table 3. Comparison of baseline characteristics among SARS-CoV-2 infected pregnant people during the pre-Delta period and Omicron dominant wave.

Variables, before matching	**Pre-delta (n=870)**	**Omicron-wave (n=77)**	***P value***	***SMD***
Maternal age (years)	29.1 ± 5.62	29.8 ± 6.04	.284	0.132
• <25	212 (24.4)	18 (23.4)	.532	0.114
• ≥25 and <38	587 (67.5)	50 (64.9)		
• ≥38	71 (8.1)	9 (11.7)		
Maternal BMI (kg/m^2)	25.3 (23.8 – 27.9)	27.4 (25.0 – 29.4)	<.001	0.315
• <25	416 (47.8)	19 (24.7)	.002	0.379
• ≥25 to <30	316 (36.3)	40 (51.9)		
• ≥30	138 (15.9)	18 (23.4)		
Gestational age at diagnosis (weeks)	29.4 (20.1 – 36.1)	36.0 (28.0 – 38.6)	<.001	0.452
Multiparous	584 (67.1)	58 (75.3)	.140	0.181
Trimester at diagnosis				
• First	115 (13.2)	6 (7.8)	.008	0.412
• Second	291 (33.5)	13 (16.9)		
• Third	464 (53.3)	58 (75.3)		
Comorbidities				
• Pre-gestational diabetes	10 (1.1)	0 (0.0)	.715	-0.152
• Pulmonary disease	11 (1.3)	0 (0.0)	.661	-0.159
• Chronic hypertension	10 (1.1)	0 (0.0)	.715	-0.152
Variables, after matching	**Pre-delta (n=308)**	**Omicron wave (n=77)**	***P value***	***SMD***
Maternal age (years)	29.4 ± 5.31	29.8 ± 6.04	.608	0.067
• <25	68 (22.1)	18 (23.4)	.373	0.057
• ≥25 and <38	218 (70.8)	50 (64.9)		
• ≥38	22 (7.1)	9 (11.7)		
Maternal BMI (kg/m^2)	26.7 (25.0 – 29.4)	27.4 (25.0 – 29.4)	.869	0.022
• <25	76 (24.7)	19 (24.7)	.999	-0.035
• ≥25 to <30	160 (51.9)	40 (51.9)		
• ≥30	72 (23.4)	18 (23.4)		

Gestational age at diagnosis (weeks)	35.2 (28.2 – 38.3)	36.0 (28.0 – 38.6)	.856	0.023
Multiparous	213 (69.1)	58 (75.3)	.288	0.137
Trimester at diagnosis				
• First	24 (7.8)	6 (7.8)	.999	0.000
• Second	52 (16.9)	13 (16.9)		
• Third	232 (75.3)	58 (75.3)		
Comorbidities				
• Pre-gestational diabetes	1 (0.3)	0 (0.0)	.999	-0.080
• Pulmonary disease	2 (0.6)	0 (0.0)	.999	-0.114
• Chronic hypertension	4 (1.3)	0 (0.0)	.706	-0.161

SMD: standardized mean difference, BMI: body mass index

Data are presented as mean ± SD, median (IQR) or number (%).

Table 4. Association of SARS-CoV-2 infection during the Omicron wave with maternal and perinatal adverse outcomes in confounder matched cohort pre-Delta wave infection.

Variables	**Pre-delta (n=308)**	**Omicron-wave (n=77)**	**RR (95% CI)***	***P value***
Maternal adverse outcomes				
• Preeclampsia	11 (3.6)	5 (6.5)	1.81 (0.65 – 5.08)	.253
• Nasal O_2 support	32 (10.4)	5 (6.5)	0.62 (0.25 – 1.55)	.251
• CPAP or high-flow O_2	15 (4.9)	4 (5.2)	1.07 (0.36 – 3.12)	.906
• Mechanical ventilation	9 (2.9)	1 (1.3)	0.44 (0.06 – 3.45)	.438
• ECMO	2 (0.6)	0 (0.0)	NE	-
• Maternal death	4 (1.3)	1 (1.3)	1.00 (0.11 – 8.82)	.999
Perinatal adverse outcomes	**Pre-delta (n=287)**	**Omicron wave (n=36)**		
• Preterm birth <37 weeks	46 (16.0)	3 (8.3)	0.52 (0.17 – 1.59)	.250
• Preterm birth <34 weeks	14 (4.9)	1 (2.8)	0.57 (0.08 – 4.20)	.580
• Stillbirth	2 (0.7)	0 (0.0)	1.99 (0.18 – 21.7)	.571

*Generalized estimating equations with log-binomial link function using matching ID as clusters.

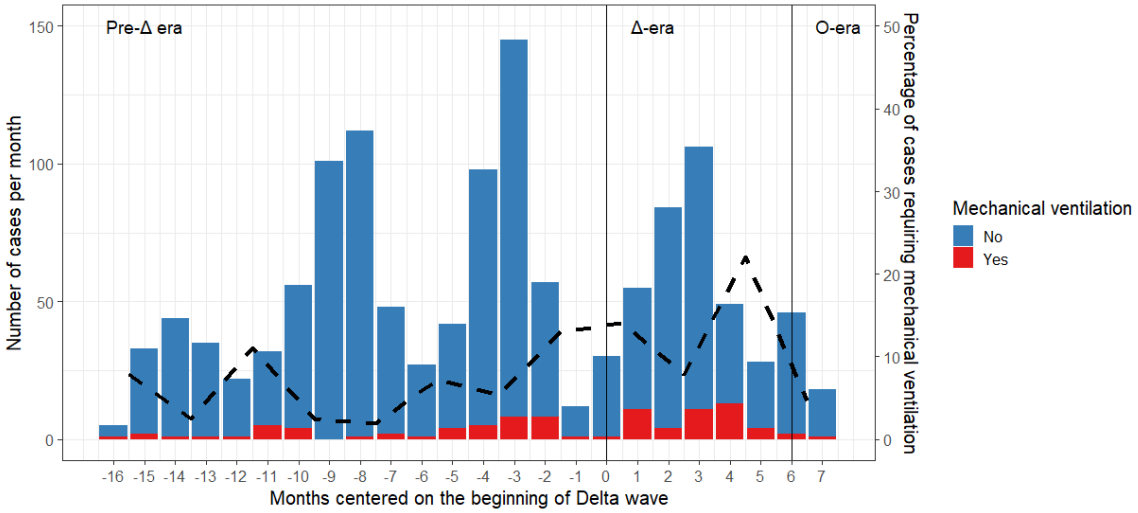
ECMO: extracorporeal membrane oxygenation, CPAP: continuous positive airway pressure, RR: risk ratio

Table 5. Factors associated with requirement for advanced respiratory support (non-invasive or invasive mechanical ventilation).

Variables	**RR (95% CI)**	**P value***	**aRR (95% CI)**	**P value**
Maternal age (years)	1.32 (1.02 – 1.63)	.006	1.21 (0.99 – 1.50)	.060
Maternal BMI (kg/m2)	1.25 (1.03 – 1.51)	.016	1.18 (0.97 – 1.42)	.078
Gestational age at diagnosis (weeks)	1.44 (1.14 – 1.85)	.002	1.36 (1.08 – 1.75)	.012
Comorbidities, any	NE	–	NE	–
Infection during the Pre-delta period	Reference	–	Reference	–
Infection during the Delta wave	2.45 (1.61 – 3.74)	<.001	2.19 (1.44 – 3.35)	<.001
Infection during the Omicron wave	1.04 (0.30 – 2.47)	.993	0.78 (0.23 – 1.95)	.644

RR: risk ratio, aRR: adjusted risk ratio, CI: confidence interval, NE: not estimable

* Generalized estimating equations with log-binomial link function using treatment centers as clusters


Pre-Δ era
Δ-era
O-era
Number of cases per month
Percentage of cases requiring mechanical ventilation
Months centered on the beginning of Delta wave
Mechanical ventilation
No
Yes