Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry

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Summary

Background SARS-CoV-2 positive pregnant women are at higher risk of adverse outcomes, but little evidence is available on how variants impact that risk. We aim to evaluate maternal and perinatal outcomes among unvaccinated pregnant women that tested positive for SARS-CoV-2, stratified by pre-Delta, Delta, and Omicron periods.

Methods This prospective study enrolled women from March 2020 to September 2022. Exposure to the different SARS-CoV-2 variants was defined by their periods of predominance. The primary outcome was severe maternal adverse outcome defined as either intensive care unit admission, acute respiratory distress syndrome, advanced

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oxygen supplementation, or maternal death. The secondary outcomes were preterm birth and other perinatal outcomes.

Findings Overall, 1402, 262, and 391 SARS-CoV-2 positive pregnant women were enrolled during the pre-Delta, Delta, and Omicron periods respectively. Severe maternal adverse outcome was reported in 3.4% (n = 947/1402; 95% confidence intervals (95%CI) 2.5–4.5), 6.5% (n = 7/262; 95%CI 3.8–10.2), and 1.0% (n = 4/391; 95%CI 0.3–2.6) of women during the pre-Delta, Delta, and Omicron periods. The risk of severe maternal adverse outcome was higher during the Delta vs pre-Delta period (adjusted risk ratio (aRR) = 1.8; 95%CI 1.1–3.2) and lower during the Omicron vs pre-Delta period (aRR = 0.3; 95%CI, 0.1–0.8). The risks of hospitalization for COVID-19 were 12.6% (n = 176/1402; 95%CI 10.9–14.4), 17.2% (n = 45/262; 95%CI 12.8–22.3), and 12.5% (n = 49/391; 95%CI 9.4–16.2), during the pre-Delta, Delta, and Omicron period, respectively. Pregnancy complications occurred after SARS-CoV-2 exposure in 30.0% (n = 363/1212; 95%CI 27.4–32.6), 35.2% (n = 83/236; 95%CI 29.1–41.6), and 30.3% (n = 105/347; 95%CI 25.5–35.4) of patients during the pre-Delta, Delta, and Omicron periods, respectively. Stillbirths were reported in 0.5% (n = 6/1159; 95%CI 0.2–1.1), 2.8% (n = 6/210; 95%CI 1.0–6.0), and 0.9% (n = 2/213; 95%CI 0.1–3.4) or patients during the pre-Delta, Delta, and Omicron periods respectively.

Interpretation The Delta period was associated with a higher risk of severe maternal adverse outcome and the Omicron period with a lower risk of severe adverse outcome compared to pre-Delta era. The reported risk of hospitalization was high during the Omicron period and should not be trivialized.

Research in context

Evidence before this study

Pregnant women that test positive for SARS-CoV-2 are at higher risk of maternal and neonatal adverse outcomes. Several variants of concern have emerged since the beginning of the pandemic. The Delta variant has been reported to be more severe compared to pre-Delta or Omicron, in adults as well as in pregnant women. However, limited data is available on the Omicron variant during pregnancy. We searched on PubMed and SSRN available as of November 3, 2022 for English articles studying severe maternal adverse outcomes following SARS-CoV-2 infection among unvaccinated pregnant women, according to the Omicron variant found few articles using the search terms "pregnancy", "pregnant women", "COVID-19", "SARS-CoV-2", "Delta" and "Omicron". The studies identified were all retrospective and the majority included both vaccinated and unvaccinated pregnant women in the same cohort. A recent Scottish study based on more than 9000 pregnancies evaluating both vaccinated and unvaccinated pregnant women, reported lower risks of maternal and pregnancy adverse outcomes in the Omicron period based on a national registry database. A study performed in Malawi, including 55 pregnant women in the fourth local wave of SARS-CoV-2 assumed to be the Omicron variant, also reported less severe maternal outcome than in previous waves, regardless of the vaccination status.

Added value of this study

Our research is the first to report results from a prospective and dedicated designed study that compared the risk of adverse maternal outcome according to the pre-Delta, Delta, and Omicron variant among unvaccinated pregnant women. The risk of severe maternal adverse outcome was lower during the Omicron period compared to the pre-Delta and Delta period. Conversely, pregnant women requiring inpatient management for COVID-19 during the Omicron period remained high.

Implications of all the available evidence

Our study reported a lower risk of severe maternal adverse outcome during the Omicron period compared to the pre-Delta and Delta periods among unvaccinated pregnant women. However, the reported risk of hospitalization for COVID-19 remained high during the Omicron period. This emphasizes the need to pursue the promotion of COVID-19 vaccination for pregnant women, especially given that the potential long-term consequences of the virus are still unknown.

Introduction

During the SARS-CoV-2 pandemic, pregnant women were reported to have a higher susceptibility to COVID-19 infection.[1] Pregnant women that tested positive for SARS-CoV-2 are at higher risk of a severe form of COVID-19, associated with higher rates of intensive care unit (ICU) admission and increased needs for respiratory support, compared to the age-matched non-pregnant population.[2,3] Women infected during pregnancy also have an increased risk of adverse pregnancy outcomes including preterm-birth, with a significant proportion secondary to iatrogenic preterm birth due to maternal illness.[3,4] Infection with SARS-CoV-2 during pregnancy has also been reported to be associated with a higher risk of stillbirth directly or indirectly caused by the virus.[5] Rare cases of confirmed viral vertical transmission have been reported, associated with critical neonatal adverse outcomes.[6,7]

SARS-CoV-2 has already mutated into five main variants of concern (VOC), as designated by the WHO. The Alpha, the Beta and the Gamma variants, were the first VOC of the pandemic (pre-Delta period), followed by the Delta variant, which was rapidly predominant, and finally replaced by the current Omicron variant.[8] The Delta variant was associated with increased COVID-19 severity, including a higher hospitalization rate and poorer clinical outcomes in the general population, compared to pre-Delta variants.[9,10] The Omicron variant has been reported to spread very rapidly with a rate of re-infection up to 15%. The severity of the disease with this variant, however, was lower, with a decreased risk of hospitalization and less clinically severe illness, regardless of previous acquired immunity status.[11–13] COVID-19 reinfection has been reported to be less severe than primary infection, making it difficult to interpret the real pathogenicity of emerging variants.[14] Similar results were observed among unvaccinated pregnant women exposed to the Delta variant during pregnancy, with a higher risk of severe disease and a higher risk of preterm birth.[15–17] Little evidence is available on the impact of the Omicron variant on unvaccinated pregnant women and it is urgent to assess the impact of this variant as COVID-19 vaccine hesitancy remains high in pregnant women despite its safety and efficacy.[18–20]

The primary aim of this study was to compare the risk of maternal adverse outcomes among unvaccinated pregnant women that tested positive for SARS-CoV-2 during one of three different periods of variant predominance: pre-Delta, Delta, and Omicron. The secondary aim was to describe the rate of preterm birth and other perinatal outcomes in women stratifying by variant predominance.

Methods

Settings

This prospective cohort study enrolled patients from March 24, 2020 to September 28, 2022, in France and Switzerland, using the COVI-PREG registry. This registry aims to evaluate the impact of SARS-CoV-2 infection among pregnant women.[21] Hospitals with an antenatal clinic and/or labor ward were able to participate in this multicenter registry. An oral and written consent was obtained from all patients included in the study. The Swiss Ethical Board (CER-VD-2020-00548) approved the study and French data was registered with the French National Data Protection Commission (CNIL - authorization 2217464).

Data collection

Pregnant women were included at the time of a positive SARS-CoV-2 test. Local investigators completed 3 different forms: 1) the enrollment form at initial inclusion documenting the patient's baseline characteristics, medical/obstetrical history, and SARS-CoV-2 exposure/testing information; 2) a first follow-up form dedicated to the COVID-19 event management and COVID-19 maternal outcomes; 3) a second follow-up form completed at the end of the pregnancy, after the patient's discharge from maternity, collecting pregnancy and neonatal outcomes. Data were collected individually from medical records and stored as de-identified data using the REDCap (Research Electronic Data Capture) online database.

Participants

Only pregnant women who tested positive for SARS-CoV-2 were included in the study. They were tested either because of symptoms compatible with COVID-19, potential SARS-CoV-2 exposure, or local universal screening protocols. Only patients with a confirmed positive nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) or an antigen test were included in the study. Patients vaccinated for COVID-19 before or during the current pregnancy were excluded. No information was available regarding any previous SARS-CoV-2 infection prior to pregnancy. Patients who were under the legal age of 18 years and/or who were not able to consent were not included.

Exposure to pre-Delta, Delta, and Omicron SARS-CoV-2 variants

As the information on specific viral strains impacting patients was not available (i.e. genome sequencing of SARS-CoV-2 was not universally performed), we assumed that a pregnant woman enrolled in the study was infected with the predominant variant of that specific period. The date of the positive SARS-CoV-2 test was used to assign the patient to one of these periods. If the date of the test was missing, the date of onset of symptoms was used.

Variant predominance was determined using the GISAID data platform. French and Swiss health

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authorities provided national relative variant frequency on a weekly basis by sequencing viral strains obtained from representative national samples.[22] Using the relative variant frequency, the three different periods of interest were defined as follows: the pre-Delta period, corresponding to the period before the emergence of the Delta variant (i.e., Alpha, Beta, Gamma), defined as the period with Delta variant infection in <20% of national samples; the Delta period, considered as the period when the Delta variant was reported in ≥80% of national samples; the Omicron period, considered as the period when the Omicron variant was reported in ≥80% of national samples. Between these periods of interest, we have defined two transition periods: the period between pre-Delta and Delta periods (>20% and <80% of Delta variant) and the period between Delta and Omicron periods (>20% and <80% of Omicron variant). The different periods are illustrated in Fig. S1 – supplementary materials. Patients who were included in COVI-PREG during the two transition periods were excluded to prevent exposure misclassification.

Maternal adverse outcomes

Maternal severe adverse outcome was a composite outcome defined as a patient experiencing at least one of the following outcomes related to COVID-19 only: ICU admission, acute respiratory distress syndrome (ARDS), high flow oxygen requirement, non-invasive ventilation requirement, or mechanical ventilation, and maternal death of any cause. Other maternal outcomes included inpatient management for the COVID-19 event (e.g., standard unit admission, ICU admission), length of stay in ICU >7 days, supplemental oxygen requirement (including standard oxygen, high-flow oxygen, non-invasive ventilation, and mechanical ventilation), and extracorporeal membrane oxygenation (ECMO) requirement. All patients included in this study were considered for this analysis.

Pre-term birth outcome

Preterm birth was defined as a birth occurring before 37 weeks of gestation (wks) and was divided into three categories: <37 wks (23–36 wks and 6 days), <32 wks (23–31 wks and 6 days), and <28 wks (23–27 wks and 6 days). Preterm birth was also categorized as either spontaneous (occurring after a spontaneous labor) or induced (medically indicated birth, after an induction of labor or a caesarean section without spontaneous labor). Iatrogenic preterm birth due to COVID-19 was defined as an induced preterm birth directly related to COVID-19 either for maternal or fetal reasons. For this analysis, only pregnancies resulting in a livebirth occurring at or after 23 wks and patients exposed to SARS-CoV-2 before 37 wks were considered. Patients with a pregnancy that did not reach an expected due date of 42 wks during the study period were also excluded to ensure only exposures who had the potential to develop the outcome of interest were included.

Pregnancy and neonatal outcomes

Pregnancy complications were defined as pregnancy related conditions that arose after the positive test (preeclampsia, gestational diabetes, intrauterine growth restriction, abnormal fetal Doppler, suspected macrosomia, threatened preterm labor, preterm premature rupture of membranes, post-partum hemorrhage). Labor was defined as either spontaneous or induced. Vaginal birth was defined as either spontaneous or assisted (i.e., by vacuum extractor, forceps). Cesarean section was defined as either emergent out of labor/induction, emergent during labor/induction, or planned out of labor. Emergency cesarean section could be directly related to COVID-19 when the reason for delivery was for a maternal or fetal indication secondary to COVID-19. Livebirth was defined as a birth of a live born neonate occurring at or after 23 wks. The delivery of a pre-viable fetus was defined as a birth occurring from 20 wks to 22 wks and 6 days without neonatal resuscitation. Stillbirth was defined as an in utero fetal demise at 20 weeks or more. Late termination of pregnancy was any medically indicated termination of pregnancy at 20 weeks or more. For this analysis, pregnant women with a known pregnancy outcome from 20 wks were included.

Neonatal weight at birth was defined as the weight in grams measured just after the delivery. Small for gestational age (SGA) was defined as a weight at birth less than 10th and intrauterine growth restriction as less than 3rd percentile for gestational age according to the INTERGROWTH charts.[23] Apgar score was collected at 5 min after birth and a poor Apgar score at 5 min was defined as less than 7. Neonatal intensive care unit (NICU) admission and neonatal death for any reason were also collected.

Co-variables

Patients' demographic characteristics were collected, including maternal age categories (≤25 years (y), 26–30 y, 31-35 y, 36–40 y, and >40 y, marital status, ethnicity, country of residence, educational level, body mass index (BMI) at inclusion (kg/m^2), medical history, addiction during pregnancy, obstetrical history including previous pregnancies complications and ongoing pregnancy characteristics, conditions arising in pregnancy before exposure to the virus. Trimester of pregnancy at infection were defined as last menstrual period date to 13 wks and 6 days for the 1st trimester, 14 wks–27 wks and 6 days for the 2nd trimester, and 28 wks until the end of pregnancy for the 3rd trimester.

Statistical analysis

Descriptive statistics were used to assess the baseline characteristics of patients and different outcomes of interest. Proportions were reported with their 95% confidence intervals (95%CI). To evaluate the association between outcomes severe adverse maternal composite outcome and the three periods of interest, we performed a univariate and a multivariate generalized linear regression model to estimate Risk Ratios (RR) with 95%CI to compare the pre-Delta versus Delta and the pre-Delta versus Omicron period. In the multivariate analysis, the model included all unbalanced baseline characteristics between groups, defined as a standardized difference (SD) of more than 10% between groups. Statistical analyses were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Results

A total of 2244 pregnant women that tested positive for SARS-CoV-2 were enrolled in COVI-PREG. The 15 and 174 patients infected during the pre-Delta/Delta and Delta/Omicron transition periods, respectively, were excluded (Table S1 supplementary materials). Overall, 2055 patients were included with 1402 patients during the pre-Delta period, 262 patients during the Delta, and 391 patients during the Omicron. Variants time periods are reported in supplementary materials Table S2.

Overall, the mean maternal age was 31.7 years with 21.9% (n = 450/2055) aged more than 35 years. Most patients were of white ethnicity (67.8%; n = 1394/2055). With regards to location, 36.8% (n = 756/2055) and 63.2% (n = 1299/2055) of patients were living in France and Switzerland respectively. Maternal BMI was above 35 kg/m^2 in 5.8% (n = 120/2055) of cases. Overall, pregnant women were infected during the first trimester in 14.4% (n = 295/2055) of cases, second in 34.6% (n = 711/2055), and third in 50.0% (1028/2050). Trimester of infection was unknown for 21 patients (1.0%). Baseline characteristics are presented according to the three periods of interest in Table 1. In three patients, the date of the SARS-CoV-2 test was missing and the date of symptom onset was used instead. All three patients had symptoms in the pre-Delta period (August 2020, January 2021, and March 2021) with no possibility of exposure misclassification.

Maternal adverse outcomes

Among patients that tested positive for SARS-CoV-2, a severe maternal adverse outcome was reported in 3.4% (n = 47/1402; 95%CI 2.5–4.5), 6.5% (n = 17/262; 95%CI 3.8–10.2), and 1.0% (n = 4/391; 95%CI 0.3–2.6) of patients during the pre-Delta, Delta, and Omicron period, respectively. ICU admission was reported in 3.2% (n = 45/1402; 95%CI 2.4–4.3) during the pre-Delta period, 5.0% (n = 13/262; 95%CI 2.7–8.3) during the Delta, and 1.0% (n = 4/391; 95%CI 0.3–2.6) during the Omicron. Mechanical ventilation was required in 0.9% (n = 14/1402; 95%CI 0.5–1.7) of patients during the pre-Delta period and 2.7% (n = 7/262; 95%CI 1.1–5.4) during the Delta period. No patients required high-flow oxygen, non-invasive ventilation, or mechanical ventilation during the Omicron period. During the pre-Delta and Delta periods, 0.9% (n = 12/1402 95%CI 0.1–1.5) and 1.9% (n = 5/262; 95%CI 0.6–4.4) of patients admitted to the ICU stayed more than 7 days, and none (0/391) during the Omicron. A total of three (n = 3/1402; 0.2%; 95%CI 0.0–0.6) maternal deaths were reported in the pre-Delta period and none in the Delta and Omicron (Table 2). Maternal deaths were directly related to extremely severe COVID-19. Maternal outcomes of patients that tested positive during the transition periods are reported in Table S3 supplementary materials.

Delta vs. pre-Delta

The Delta period was associated with more severe maternal adverse outcomes when compared to the pre-Delta period, with a crude RR of 1.9 (95%CI, 1.1–3.3). This association persisted after adjustment for the unbalanced potential confounders, with an adjusted risk ratio (aRR) of 1.8 (95%CI 1.1–3.2) for severe adverse maternal outcome during the Delta period, compared to the pre-Delta one (Table 3).

Omicron vs pre-Delta

The Omicron period was associated with fewer severe maternal adverse outcomes compared to the pre-Delta, with a crude RR of 0.3 (95%CI, 0.1–0.8) and an aRR of 0.3 (95%CI, 0.1–0.8) after adjustment for the unbalanced potential confounders (Table 3).

Preterm birth outcomes

A total of 1544 pregnant women with a pregnancy resulting in a livebirth at 23 weeks or later were exposed to SARS-CoV-2 before 37 wks. Patient characteristics are presented in Table S4 supplementary materials. Overall, 993 patients were included during the pre-Delta period, 168 during the Delta, and 245 during the Omicron. Preterm birth less than 37 wks occurred in 9.3% (n = 92/993; 95%CI 7.5–11.2) of patients during the pre-Delta period, 13.7% (n = 23/168; 95%CI 8.9–20.5) during the Delta, and 11.0% (n = 27/245; 95%CI 7.4–15.6) during the Omicron. Preterm birth less than 32 wks occurred in 2.0% (n = 19/993; 95%CI, 1.2–3.1), 4.8% (n = 8/168; 95%CI 2.1–9.2), and 2.0% (n = 5/245; 95%CI 0.7–4.7) of patients during the pre-Delta, Delta, and Omicron periods, respectively. Extremely preterm birth less than 28 wks occurred in 0.6% (n = 6/993; 95%CI 0.2–1.4) and in 0.8% (n = 2/245; 95%CI 0.1–2.9) of patients during the pre-Delta and Omicron periods, respectively and none during the Delta (Table 4).

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	Pre-Delta n = 1402		Delta n = 262			Omicron n = 391		
	n	%	n	%	Std. Diff.	n	%	Std. Diff.
Maternal age at first dose - n %								
≤25	148	10.6%	28	10.7%	−0.4	41	10.5%	0.2
26-30	421	30.0%	76	29.0%	2.2	117	29.9%	0.2
31-35	520	37.1%	98	37.4%	−0.7	145	37.1%	0.0
36-40	243	17.3%	49	18.7%	−3.6	70	17.9%	−1.5
>40	63	4.5%	9	3.4%	5.4	16	4.1%	2.0
Missing	7	0.5%	2	0.8%	−3.3	2	0.5%	−0.2
Marital status - n %								
Married or domestic partnership	1187	84.7%	222	84.7%	−0.2	325	83.1%	4.2
Single never married	126	9.0%	30	11.5%	−8.1	25	6.4%	9.7
Divorced or separated	14	1.0%	2	0.8%	2.5	6	1.5%	−4.8
Unknown	36	2.6%	4	1.5%	7.4	9	2.3%	1.7
Missing	39	2.8%	4	1.5%	8.7	26	6.6%	−18.3
Ethnicity - n %								
White	947	67.5%	181	69.1%	−3.3	266	68.0%	−1.0
Hispanic or Latino	55	3.9%	6	2.3%	9.4	11	2.8%	6.2
Black or African American	156	11.1%	32	12.2%	−3.4	38	9.7%	4.6
Asian or Pacific islander	50	3.6%	3	1.1%	16.0	12	3.1%	2.8
Other	67	4.8%	22	8.4%	−14.6	15	3.8%	4.6
Unknown	75	5.3%	11	4.2%	5.4	20	5.1%	1.1
Missing	52	3.7%	7	2.7%	5.9	29	7.4%	−16.2
Country of residence - n %								
France	531	37.9%	92	35.1%	5.7	133	34.0%	8.0
Switzerland	871	62.1%	170	64.9%	−5.7	258	66.0%	−8.0
Educational level - n %								
University/college or equivalent	467	33.3%	68	26.0%	16.2	128	32.7%	1.2
Intermediate	212	15.1%	55	21.0%	−15.3	84	21.5%	−16.5
Secondary school	116	8.3%	31	11.8%	−11.9	22	5.6%	10.4
Primary school or less	18	1.3%	3	1.1%	1.3	2	0.5%	8.2
Unknown	503	35.9%	95	36.3%	−0.8	120	30.7%	11.0
Missing	86	6.1%	10	3.8%	10.7	35	9.0%	−10.7
Maternal BMI (kg/m2) - n %								
BMI >30	266	19.0%	49	18.7%	0.7	58	14.8%	11.1
BMI >35	93	6.6%	11	4.2%	10.8	16	4.1%	11.3
Maternal addiction								
Any	85	6.2%	21	8.2%	−7.5	29	7.9%	−6.5
Drug	3	0.2%	3	1.1%	−11.4	2	0.5%	−5.0
Tobacco	76	5.4%	19	7.3%	−7.5	28	7.2%	−7.2
Alcohol	9	0.6%	1	0.4%	3.6	5	1.3%	−6.5
Obstetrical history								
Nulliparous	604	43.1%	101	38.5%	9.2	191	48.8%	−11.6
Previous cesarean section	233	16.6%	38	14.5%	5.8	45	11.5%	14.7
Medical history								
Pulmonary	38	2.7%	3	1.1%	11.4	9	2.3%	2.6
Cardiac	13	0.9%	6	2.3%	−10.8	9	2.3%	−10.9
Hypertensive	24	1.7%	4	1.5%	1.5	6	1.5%	1.4
Diabetes	19	1.4%	4	1.5%	−1.4	1	0.3%	12.3
Immunosuppression	6	0.4%	0	0.0%	9.3	0	0.0%	9.3
Neurological	15	1.1%	8	3.1%	−14.0	5	1.3%	−1.9
Digestive	19	1.4%	0	0.0%	16.6	1	0.3%	12.3
Renal	10	0.7%	3	1.1%	−4.5	4	1.0%	−3.3

(Table 1 continues on next page)

	Pre-Delta			Delta			Omicron		
	n = 1402			n = 262			n = 391		
	n	%		n	%	Std. Diff.	n	%	Std. Diff.
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Urological	13	0.9%		1	0.4%	6.8	1	0.3%	8.8
Oncological	9	0.6%		1	0.4%	3.6	1	0.3%	5.8
Thyroid imbalance	59	4.2%		13	5.0%	−3.6	14	3.6%	3.2
Other	189	13.5%		36	13.7%	−0.8	52	13.3%	0.5
No comorbidities	988	70.5%		183	69.8%	1.4	288	73.7%	−7.1
Previous pregnancy complications									
Preeclampsia	18	1.3%		4	1.5%	−2.1	4	1.0%	2.4
Intrauterine growth restriction	30	2.1%		4	1.5%	4.6	3	0.8%	11.5
Fetal malformation	17	1.2%		2	0.8%	4.5	2	0.5%	7.6
Preterm birth	23	1.6%		3	1.1%	4.2	1	0.3%	14.3
Postpartum hemorrhage	26	1.9%		16	6.1%	−21.9	11	2.8%	−6.4
Other	86	6.1%		23	8.8%	−10.1	24	6.1%	0.0
None	1202	85.7%		210	80.2%	14.9	346	88.5%	−8.2
Ongoing pregnancy									
Singletons	1372	97.9%		259	98.9%	−7.8	382	97.7%	1.1
Twins	30	2.1%		3	1.2%	7.1	9	2.3%	−1.4
Ongoing pregnancy condition (before exposure to the virus)									
Preeclampsia	13	0.9%		1	0.4%	6.8	2	0.5%	4.9
Gestational diabetes	145	10.3%		22	8.4%	6.7	29	7.4%	10.3
Intrauterine growth restriction	29	2.1%		2	0.8%	11.1	5	1.3%	6.2
Abnormal fetal Doppler	6	0.4%		0	0.0%	9.3	1	0.3%	3.0
Macrosomia	13	0.9%		2	0.8%	1.8	3	0.8%	1.7
Threatened preterm labor	15	1.1%		6	2.3%	−9.5	7	1.8%	−6.1
Placenta praevia	8	0.6%		2	0.8%	−2.4	0	0.0%	10.7
PPROM	8	0.6%		1	0.4%	2.7	1	0.3%	4.9
Other	107	7.6%		18	6.9%	2.9	33	8.4%	−3.0
None	1058	75.5%		208	79.4%	−9.4	310	79.3%	−9.1
EXPOSURE - Trimester of infection									
Trimester 1	253	18.0%		15	5.7%	38.8	27	6.9%	34.2
Trimester 2	517	36.9%		85	32.4%	9.3	109	27.9%	19.3
Trimester 3	628	44.8%		157	59.9%	−30.6	243	62.1%	−35.3
Unknown	4	0.3%		5	1.9%	−15.6	12	3.1%	−21.8

BMI: body mass index, PPROM: preterm premature rupture of membranes.

Table 1: Patient characteristics according to the variant time periods.

Maternal outcomes and pregnancy conditions following SARS-CoV-2 exposure as well as mode of delivery according to the periods of interest are presented in supplementary materials Table S5. Preterm birth outcomes as well as maternal/pregnancy outcomes and mode of delivery for transition periods are reported in supplementary materials Table S6.

Pregnancy and neonatal outcomes

Pregnancy outcomes

A total of 1964 pregnancies that tested positive for SARS-CoV-2 had a known pregnancy outcome from 20 wks onwards. Patient characteristics and maternal outcomes are presented in the supplementary materials Tables S7 and S8 respectively. Overall, 1212 patients were included during the pre-Delta period, 236 during the Delta, and 347 during the Omicron. Pregnancy complications arising after COVID-19 infection were reported in 30.0% (n = 363/1212; 95%CI 27.4–32.6), 35.2% (n = 83/236; 95%CI 29.1–41.6), and 30.3% (n = 105/347; 95%CI 25.5–35.4) of patients during the pre-Delta, Delta, and Omicron periods, respectively (Table 5). Stillbirths were reported in 0.5% (n = 6/1159; 95% CI 0.2–1.1), 2.8% (n = 6/210; 95%CI 1.0–6.0), and 0.9% (n = 2/213; 95%CI 0.1–3.4) of patients during the pre-Delta, Delta, and Omicron periods respectively (Table 5).

Articles

	Pre-Delta			Delta			Omicron		
	n = 1402			n = 262			n = 391		
	n	%	95%CI	n	%	95% CI	n	%	95% CI
Maternal adverse outcome	**47**	**3.4%**	2.5–4.4	**17**	**6.5%**	3.8–10.2	**4**	**1.0%**	0.3–2.6
Inpatient management	176	**12.6%**	10.9–14.4	45	**17.2%**	12.8–22.3	49	**12.5%**	9.4–16.2
Standard unit	131	**9.3%**	7.9–11.0	32	**12.2%**	8.5–16.8	45	**11.5%**	8.5–15.1
ICU admission	45	**3.2%**	2.4–4.3	13	**5.0%**	2.7–8.3	4	**1.0%**	0.3–2.6
Length ICU >7 days	12	**0.9%**	0.4–1.5	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9
Maternal complications									
Pneumonia	33	**2.4%**	1.6–3.3	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9
ARDS	56	**4.0%**	3.0–5.2	8	**3.1%**	1.3–5.9	0	**0.0%**	0.0–0.9
Oxygen supply requirement	66	**4.7%**	3.7–6.0	26	**9.9%**	6.6–14.2	2	**0.5%**	0.1–1.8
Standard oxygen	35	**2.5%**	1.7–3.5	13	**5.0%**	2.7–8.3	2	**0.5%**	0.1–1.8
High Flow oxygen	12	**0.9%**	0.4–1.5	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9
Non-invasive ventilation	5	**0.4%**	0.1–0.8	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9
Mechanical ventilation	14	**1.0%**	0.5–1.7	7	**2.7%**	1.1–5.4	0	**0.0%**	0.0–0.9
ECMO	7	**0.5%**	0.2–1.0	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9
Maternal death (any reason)	3	**0.2%**	0.0–0.6	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9

ICU: intensive care unit, ARDS: acute respiratory distress syndrome, ECMO: extracorporeal membrane oxygenation.

Table 2: Maternal adverse outcomes among pregnant women tested positive for SARS-CoV-2 according to the pre-Delta, Delta, and Omicron periods.

Neonatal outcomes

A total of 1226, 233, and 352 livebirths were recorded during the pre-Delta, Delta, and Omicron periods, respectively. Small weight for gestational age was reported in 6.9% (n = 85/1226; 95%CI 5.6–8.5), 4.7% (n = 11/233; 95%CI 2.4–8.3), and 6.0% (n = 21/352; 95% CI 3.7–9.0) of neonates for the pre-Delta, Delta, and Omicron periods respectively. Apgar scores less than 7 were reported in 3.2% (n = 39/1226; 95%CI 1.3–3.1), 2.9% (n = 6/233; 95%CI 1.1–6.1), and 2.3% (n = 9/352; 95%CI 0.8–5.4) of neonates during the pre-Delta, Delta, and Omicron periods (Table 5). Four (0.4%; n = 4/1226; 95%CI 01–0.8) neonates died, during the pre-Delta period and two (0.6%; 2/352; 95%CI 0.1–2.0 during the Omicron (Supplementary materials Table S9). Maternal, pregnancy, and neonatal outcomes for transition periods are presented in supplementary materials Table S10.

Discussion

This study showed that the risk for a severe maternal adverse outcome differed between time periods associated with specific SARS-CoV-2 variant predominance with a risk of 3.4%, 6.5%, and 1.0% during the pre-Delta, Delta, and Omicron periods, respectively.

In this study, the Delta variant period was associated with a higher risk of severe maternal adverse outcome compared to the pre-Delta period. Pregnant women that tested positive during the Delta period had trends of higher risks of hospitalization, ICU admission, and advanced oxygen requirements than during the pre-Delta period. Similar results were reported in the unvaccinated general population with a significantly higher risk of hospitalization and presentation to emergency care in patients that tested positive for the Delta compared to pre-Delta variants.[9,24] Our results are also consistent with the current literature regarding the Delta variant that reported higher risk of adverse maternal outcomes including oxygen requirements, hospitalization, and ICU admission.[15–17] The Delta variant remains the variant with the highest pathogenicity potential to date.

Our results show that the Omicron variant period was associated with a lower risk of severe maternal adverse outcome and a lower risk of ICU admission compared to pre-Delta. This could be interpreted to suggest that Omicron variant induces less severe disease during pregnancy, compared to the previous SARS-CoV-2 strains. Conversely, in our study, pregnant women requiring inpatient management for COVID-19 during the Omicron period remained high with 12.5% of patients needing hospitalization. Nevertheless, no advanced oxygen supplementation was required for these patients and the risk of ICU admission (1%) was lower than during the pre-Delta (3.2%) or Delta (5.0%) periods. Additionally, none of the women that tested positive during the Omicron period were admitted to the ICU for more than 7 days, suggesting that Omicron induced a less severe disease. These results are consistent with the already published data that reported a less severe disease during the Omicron period in unvaccinated adults with a reduced risk of severe disease compared with previous strains.[25] Our results confirmed already published data on pregnant women reporting a trend of a less severe disease during the Omicron

	Pre-Delta			Delta			Omicron			Delta Vs Pre-Delta				Omicron Vs Pre-Delta			
	n = 1402			n = 262			n = 391										
	n	%	95%CI	n	%	95%CI	n	%	95%CI	Crude RR	95%CI	adj. RR[a]	95%CI	Crude RR	95%CI	adj. RR[b]	95%CI
Severe maternal adverse outcome	47	**3.4%**	2.5–4.4	17	**6.5%**	3.8–10.2	4	**1.0%**	0.3–2.6	**1.9**	**1.1–3.3**	**1.8**	**1.1–3.2**	**0.3**	**0.1–0.8**	**0.3**	**0.1–0.8**
ICU admission	45	**3.2%**	2.4–4.3	13	**5.0%**	2.7–8.3	4	**1.0%**	0.3–2.6	–	–	–	–	–	–	–	–
Length of ICU admission >7 days	12	**0.9%**	0.4–1.5	5	**1.9%**	0.6–4.4	0	**0.0%**	0.0–0.9	–	–	–	–	–	–	–	–
High Flow oxygen	12	**0.9%**	0.4–1.5	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9	–	–	–	–	–	–	–	–
Non-invasive ventilation	5	**0.4%**	0.1–0.8	3	**1.1%**	0.2–3.3	0	**0.0%**	0.0–0.9	–	–	–	–	–	–	–	–
Mechanical ventilation	14	**1.0%**	0.5–1.7	7	**2.7%**	1.1–5.4	0	**0.0%**	0.0–0.9	–	–	–	–	-	–	–	–
Maternal death (any reason)	4	**0.3%**	0.1–0.7	0	**0.0%**	0.0–1.4	0	**0.0%**	0.0–0.9	–	–	–	–	–	–	–	–

In bold: 95% CI does not includes 1. RR: risk ratio, adj. RR: adjusted risk ratio, ICU: intensive care unit. [a]Adjusted for ethnicity, educational level, BMI >35 kg/m², drug use, pulmonary, cardiac, neurological and digestive medical history, previous pregnancy with post-partum hemorrhage or other complication, ongoing pregnancy with intrauterine growth restriction, and trimester of infection. [b]Adjusted for marital status, ethnicity, educational level, BMI >30 kg/m², nulliparity, history of cesarean section, cardiac, diabetes, and digestive medical history, previous pregnancy with intrauterine growth restriction or preterm birth, current pregnancy with gestational diabetes or placenta praevia, and trimester of infection.

Table 3: Association of Delta vs. pre-Delta and Omicron vs pre-Delta periods of infection with adverse maternal outcomes.

period, with lower rates of oxygen requirement.[16] Additionally, a recent nationwide study from Scotland reported a significantly lower rate of critical care admission, adjusted by vaccination status, among pregnant women who tested positive for COVID-19, regardless of the indication of admission.[17] Acquired immunity from previous SARS-CoV-2 infections and improved management of pregnant women infected with SARS-CoV-2 over time might partially explain the decreased risk observed in our study during the Omicron period.

Preterm birth prior to 37 wks among patients that tested positive for SARS-CoV-2 remained high, with reported rates of 9.3%, 13.7%, and 11% in the pre-Delta, Delta, and Omicron periods respectively remain higher than the national rates (5–7% in the previous years).[26,27] Nevertheless, the infection itself may induces systemic inflammatory mechanisms that could lead to higher risks of preterm birth as observed in other systemic infections during pregnancy.[28] Regardless of the period of interest, low rates of adverse neonatal were reported.

The strength of this research is its prospective design and the large number of patients included in each period of interest with high quality and detailed data, and brings very timely evidence. However, several points limit the interpretation. First, the centers participating in the COVI-PREG registry were regional/university hospitals. This may have introduced a selection bias in the recruitment of patients, such as more severe patients who needed hospital care or dedicated maternity level admission but also in selecting patient with higher comorbidities as they have required care in antenatal clinics as previously observed.[3,19] Our study population is thus, probably, not representative of the

	Pre-Delta			Delta			Omicron		
	n = 993			n = 168			n = 245		
	n	%	95%CI	n	%	95%CI	n	%	95%CI
PREMATURITY (<37 weeks)	92	**9.3%**	7.5–11.2	23	**13.7%**	8.9–19.8	27	**11.0%**	7.4–15.6
- Spontaneous	33	**3.3%**	2.3–4.6	7	**4.2%**	1.7–8.4	10	**4.1%**	2.0–7.4
- Iatrogenic birth directly related to COVID-19	15	**1.5%**	0.8–2.5	7	**4.2%**	1.7–8.4	0	**0.0%**	0.0–1.5
<32 weeks	19	**2.0%**	1.2–3.1	8	**4.8%**	2.1–9.2	5	**2.0%**	0.7–4.7
- *Spontaneous*	6	**0.6%**	0.2–1.4	2	**1.2%**	0.1–4.2	1	**0.4%**	0.0–2.3
- *Iatrogenic birth directly related to COVID-19*	4	**0.4%**	0.1–1.1	2	**1.2%**	0.1–4.2	0	**0.0%**	0.0–1.5
<28 weeks	6	**0.6%**	0.2–1.4	0	**0.0%**	0.0–2.2	2	**0.8%**	0.1–2.9
- *Spontaneous*	1	**0.1%**	0.0–0.6	0	**0.0%**	0.0–2.2	1	**0.4%**	0.0–2.3
- *Iatrogenic birth directly related to COVID-19*	1	**0.1%**	0.0–0.6	0	**0.0%**	0.0–2.2	0	**0.0%**	0.0–1.5

In bold: 95% CI does not includes 1.

Table 4: Preterm birth outcomes according to the variants' periods among patients exposed to SARS-CoV-2 before 37 weeks of gestation with a pregnancy resulting in a livebirth after 23 weeks of pregnancy.

Articles

	Pre-Delta n = 1212			Delta n = 236			Omicron n = 347		
	N	%	95%CI	n	%	95%CI	n	%	95%CI
Pregnancy complications (after viral exposure)	**363**	**30.0%**	27.4–32.6	**83**	**35.2%**	29.1–41.6	**105**	**30.3%**	25.5–35.4
Preeclampsia	35	2.9%	2.0–4.0	7	3.0%	1.2–6.0	8	2.3%	1.0–4.5
Gestational Diabetes	111	9.2%	7.6–10.9	28	11.9%	8.0–16.7	41	11.8%	8.6–15.7
Intrauterine growth restriction	56	4.6%	3.5–6.0	12	5.1%	2.7–8.7	13	3.7%	2.0–6.3
Abnormal fetal Doppler	8	0.7%	0.3–1.3	2	0.8%	0.1–3.0	2	0.6%	0.1–2.1
Suspected macrosomia	24	2.0%	1.3–2.9	5	2.1%	0.7–4.9	12	3.5%	1.8–6.0
Threatened preterm labor	38	3.1%	2.2–4.3	9	3.8%	1.8–7.1	9	2.6%	1.2–4.9
Preterm Premature Rupture Of Membranes	23	1.9%	1.2–2.8	5	2.1%	0.7–4.9	7	2.0%	0.8–4.1
Post-partum hemorrhage	12	1.0%	0.5–1.7	1	0.4%	0.0–2.3	2	0.6%	0.1–2.1
Other	127	10.5%	8.8–12.3	28	11.9%	8.0–16.7	31	8.9%	6.2–12.4
Labour									
Spontaneous	633	**52.2%**	49.4–55.1	123	52.1%	45.5–58.6	185	53.3%	47.9–58.7
Induction of labor	353	29.1%	26.6–31.8	68	28.8%	23.1–35.0	113	32.6%	27.7–37.8
Cesarean out of labor/induction	206	17.0%	14.9–19.2	39	16.5%	12.0–21.9	45	13.0%	9.6–17.0
Unknown	20	1.7%	1.0–2.5	6	2.5%	0.9–5.5	4	1.2%	0.3–2.9
Mode of delivery									
Vaginal birth	**835**	**68.9%**	66.2–71.5	**169**	**71.6%**	65.4–77.3	**261**	**75.2%**	70.3–79.7
- Assisted	**109**	**9.0%**	7.4–10.7	**20**	**8.5%**	5.3–12.8	**32**	**9.2%**	6.4–12.8
Cesarean section	**357**	**29.5%**	26.9–32.1	**61**	**25.8%**	20.4–31.9	**82**	**23.6%**	19.3–28.5
- Emergency during labor/induction	**151**	**12.5%**	10.7–14.5	**22**	**9.3%**	5.9–13.8	**37**	**10.7%**	7.6–14.4
- Emergency out of labor	**52**	**4.3%**	3.2–5.6	**5**	**2.1%**	0.7–4.9	**13**	**3.7%**	2.0–6.3
Related directly to COVID-19	23	1.9%	1.2–2.8	12	5.1%	2.7–8.7	1	0.3%	0.0–1.6
- Planned cesarean section	**154**	**15.5%**	13.317.9	**34**	**14.4%**	10.2–19.5	**32**	**9.2%**	6.4–12.8
Unknown	20	1.7%	1.0–2.5	6	2.5%	0.9–5.5	4	1.2%	0.3–2.9
Prematurity									
<37 weeks	108	**8.9%**	7.4–10.7	32	**13.6%**	9.5–18.6	32	**9.2%**	6.4–12.8
- Spontaneous	35	2.9%	2.0–4.0	9	3.8%	1.8–7.1	9	2.6%	1.2–4.9
- Iatrogenic birth related directly to COVID-19	16	1.3%	0.8–2.1	7	3.0%	1.2–6.0	0	0.0%	0.0–1.1
<32 weeks	30	2.5%	1.7–3.5	13	**5.5%**	3.0–9.2	8	2.3%	1.0–4.5
- Spontaneous	6	0.5%	0.2–1.1	2	0.8%	0.1–3.0	2	0.6%	0.1–2.1
- Iatrogenic birth related directly to COVID-19	5	0.4%	0.1–1.0	2	0.8%	0.1–3.0	0	0.0%	0.0–1.1
<28 weeks	13	1.1%	0.6–1.8	2	0.8%	0.1–3.0	4	1.2%	0.3–2.9
- Spontaneous	6	0.5%	0.2–1.1	2	0.8%	0.1–3.0	2	0.6%	0.1–2.1
- Iatrogenic birth related directly to COVID-19	2	0.2%	0.0–0.6	0	0.0%	0.0–1.6	0	0.0%	0.0–1.1
Pregnancy outcomes									
Number of fetuses	n = 1238			n = 239			n = 356		
Livebirths	1226	99.0%	98.3–99.5	233	97.5%	94.6–99.1	352	98.9%	97.1–99.7
Pre-viable fetus birth (≥20 and < 24 weeks)	4	0.3%	0.1–0.8	0	0.0%	0.0–1.5	1	0.3%	0.0–1.6
Late termination of pregnancy (≥20 weeks	2	0.2%	0.0–0.6	0	0.0%	0.0–1.5	1	0.3%	0.0–1.6
Stillbirths	6	0.5%	0.2–1.1	6	2.5%	0.9–5.4	2	0.6%	0.1–2.0
Neonatal outcomes	n = 1226			n = 233			n = 352		
Weight at birth (mean in g.; SD)	3226	**609**		3226	**675**		3246	**596**	
<10th percentile for gestational age[a]	85	6.9%	5.6–8.5	11	4.7%	2.4–8.3	21	6.0%	3.7–9.0
<3rd percentile for gestational age[a]	25	2.0%	1.3–3.0	3	1.3%	0.3–3.7	3	0.9%	0.2–2.5
Apgar score 5 min (mean; SD)	9.5	**1.1**		9.4	**1.2**		9.5	**1.1**	
Apgar score <7	39	3.2%	2.3–4.3	6	2.6%	1.0–5.5	9	2.6%	1.2–4.8
NICU admission	153	**12.5%**	10.7–14.5	23	**9.9%**	6.4–14.4	34	**9.7%**	6.8–13.2
Neonatal death	4	**0.3%**	0.1–0.8	0	**0.0%**	0.0–1.6	2	**0.6%**	0.1–2.0

In bold: 95% CI does not includes 1. PPROM: preterm premature rupture of membranes, NICU: neonatal intensive care unit admission, SD: standard deviation. [a]Neonatal weight <10th and <3rd percentile defined according to the INTERGROWTH 21st scale (Villar J, Giuliani F, Bhutta ZA et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. The Lancet Global Health 2015; 3(11):e681–91).

Table 5: Pregnancy and neonatal outcomes according to the variant time period among patients exposed to SARS-CoV-2 with a known pregnancy outcome from 20 weeks of gestation.

entire pregnancy population. Through the registry, we did not have access to information regarding the indication for the SARS-CoV-2 test (e.g., symptoms compatible with COVID-19, routine screening) or the location of the test (e.g., hospital, pharmacy, or community). This may have impacted our results as SARS-CoV-2 testing may have changed over time and therefore could have introduced a selection bias if testing patterns selected a differential proportion of more severe or less severe women from one period to the next. Additionally, we did not have access to the sequencing of the SARS-CoV-2 variant that caused the infection in our patients, and we assumed that a woman infected during the predominant variant's period was infected by this predominant variant. No clear standard exists to define variant time periods using variant predominance to ensure accurate allocation of individuals to specific variants. The Centers for Disease Control (CDC) defines predominance of a variant as accounting for more than 50% of national circulating SARS-CoV-2 linages among infections.[29–31] Within the literature, variant predominance is defined between 70 and 95% of the samples of interest. As such, we selected an empirical threshold of 80% for predominance identified in national samples in order to ensure a relatively high threshold per specific period without excluding too many patients. For this reason, there is a potential for exposure misclassification as up to 20% of patients might had an infection to another variant then the one they have been classified for. This may have caused exposure misclassification. Furthermore, the study did not collect the immune status of women who could have been infected prior to the pregnancy, influencing the severity of the current reinfection during the pregnancy, and may have underestimated the real risk of the Delta or Omicron variants for non-immune individuals. Prior to the Omicron wave, COVID-19 reinfection in adults has been reported to have 90% lower odds of leading to hospitalization or death compared to primary infection among unvaccinated individuals.[14] The risk of SARS-CoV-2 re-infection has been reported to be up to 15% in a population including both vaccinated and unvaccinated adults.[32] In a study from Denmark, the rate of hospitalized in re-infected adults was 0.16% compared to 1.33% in primary infected individuals, with a significant adjusted hazard ratio of 0.13 (95%CI 0.03–0.54).[33] Finally, the outcome defined as ICU admission is difficult to standardized as it is subject to variability in clinician choices and local management protocols. No clear standards were available to guide clinicians on timing of and need for admission to the ICU. The management of pregnant women during the Omicron wave could have been influenced by the previous Delta wave as it was associated with more severe adverse maternal outcomes prompting a tendency for additional precautions.

This study presents evidence on maternal adverse outcomes of SARS-CoV-2 variants during pregnancy with less severe disease associated with the Omicron strain. However, our results support Nealon et al.[34] stating that Omicron severity is "milder but not mild". Omicron was reported to still induce a high risk of hospitalization and should not be trivialized. Our results should be interpreted carefully as widespread disease could potentially severely affect pregnant women. As the pandemic is not over, a new viral strain with a potentially more severe impact on pregnancy outcomes may emerge in the future. Furthermore, very scarce information is available regarding long-term implications of COVID-19 in pregnant women, such as long COVID-19 following infection during pregnancy and the potential impact of the virus on the development of infants born from mothers exposed to COVID-19 during pregnancy.[35] Thus, health care providers and public health authorities should not be complacent about COVID-19 infection during pregnancy. Focus should be placed on promoting vaccination against COVID-19 in pregnant women, before and during pregnancy, as many remain reluctant to vaccinate while pregnant.[18]

In conclusion, pregnant women exposed to SARS-CoV-2 during the Delta period, attending an antenatal clinic, were at higher risk of severe maternal outcomes with increased ICU admissions and increased need for advanced oxygen support, compared to pre-Delta and Omicron variants. Omicron was associated with less severe maternal adverse outcome. Nevertheless, the rate of hospitalization remained high with Omicron, emphasizing the need to pursue the promotion of COVID-19 vaccination for pregnant women.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2022.100569.

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