International Journal of Infectious Diseases 146 (2024) 107157

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Variability in COVID-19 symptom presentation during pregnancy and its impact on maternal and infant outcomes across the pandemic

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ARTICLE INFO

Article history:
Received 17 April 2024
Revised 21 June 2024
Accepted 24 June 2024

Keywords:
COVID-19
SARS-CoV2 variant
Symptoms
Prematurity
Intensive care unit

ABSTRACT

Background: With the dominance of different SARS-CoV-2 variants, the severity of COVID-19 has evolved. We aimed to investigate the difference in symptom prevalence and the association between symptoms and adverse pregnancy outcomes during the dominance of Wild-type/Alpha, Delta, and Omicron.
Methods: COVID-19 related symptom prevalence, maternal and specific neonatal outcomes of 5431 pregnant women registered in this prospective study were compared considering the dominant virus variant. Logistic regression models analyzed the association between specific symptoms and intensive care unit (ICU) admission or preterm birth.
Results: Infection with the Delta variant led to an increase in the symptom burden compared to the Wild-type/Alpha variant and the highest risk for respiratory tract symptoms, feeling of sickness, headache, and dizziness/drowsiness. An infection with the Omicron variant was associated with the lowest risk of dyspnea and changes in smell/taste but the highest risk for nasal obstruction, expectoration, headaches, myalgia, and fatigue compared to the Wild-type/Alpha and Delta variant dominant periods. With the progression of the Wild-type/Alpha to the Delta variant neonatal outcomes worsened. Dyspnea and fever were strong predictors for maternal ICU admission and preterm birth independent of vaccination status or trimester of infection onset.
Conclusion: The symptom burden increased during the Delta period and was associated with worse pregnancy outcomes than in the Wild-type/Alpha area. During the Omicron dominance there still was a high prevalence of less severe symptoms. Dyspnea and fever can predict a severe maternal illness.

Introduction

Infection with SARS-CoV-2 is correlated with evolving symptom profiles across different variants within the general population [1,2]. As specific variants become dominant, the severity of COVID-19 has shown fluctuations. These changes in symptom prevalence and disease severity also appear to be evident among pregnant women. Specifically, the Delta variant has been associated with increased disease severity leading to an increased likelihood of requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation compared to the Wild-type virus compared to the Wild-type virus [3]. Conversely, infection with the Omicron variant has led to fewer cases of critical illness with a reduced requirement for oxygen supplementation and a decreased risk of maternal ICU admission [4]. Nevertheless, it's important to note that Omicron still presents a significant risk for pregnant woman. Vaccination has been shown to reduce the risk of adverse maternal and neonatal outcomes such as preterm birth [5–7].

However, detailed published reports of largescale study cohorts examining symptom prevalence concerning the various dominant variants, the correlation between symptoms and pregnancy outcomes, and their comparison of timing of infection during gestation and vaccination statuses remain lacking. Existing studies predominantly focus on specific periods of the pandemic with limited case numbers and emphasize serious events such as ICU

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https://doi.org/10.1016/j.ijid.2024.107157

admissions. Detailed published reports examining symptom prevalence concerning the various dominant variants, as well as the correlation between symptoms and pregnancy outcomes remain lacking.

Hence, our objective was to quantify the variations in symptoms across three distinct periods of the pandemic, encompassing the prevalence of the Wild-type/Alpha, Delta, and Omicron variants. Additionally, we sought to explore their correlation with adverse COVID-associated morbidity and to examine pregnancy outcomes in relation to the emergence of different variants and vaccination status.

Material and methods

Study design, setting, and data collection

For this project, we utilized data from the CRONOS study (Covid-19-Related Obstetric and Neonatal Outcome Study), a multicenter prospective observational study conducted in Germany and Austria [8]. Data on pregnant women, whether presenting with acute SARS-CoV-2 infection or previous infection during pregnancy, were collected by 130 hospitals from March 2020 to December 2022, and entered into a reporting form developed using a cloud-based data platform (castoredc.com, Amsterdam, Netherlands). Each patient gave written informed consent. The study was approved by the ethics committee of the study center in Kiel (University Hospital Schleswig-Holstein in Kiel, file number D 451/20) and each participating hospital respectively. Information on the study is available at www.dgpm-online.org and from the German Clinical Trials Registry (DRKS00021208).

Study cohort

The inclusion criteria for the study were pregnancy, presence of symptomatic COVID disease and assignability to a specific virus variant with ≥80% probability. The occurrence probabilities for each variant (Wild-type/Alpha, Delta, Omicron) were assigned to each dataset using the weekly relative variant frequency data from the national database of the Robert Koch Institute (RKI), with the dominant variant at the time being assigned to each participant [9]. Cases with less than 80% probability of being assigned to a specific variant were excluded to avoid exposure misclassification during transitional periods between variant dominance. Only symptomatic women, which was defined as presenting with at least one symptom, were included in the final analysis.

COVID-19 associated symptoms

Symptoms of a SARS-CoV-2 infection concerning respiratory tract, in detail dyspnea, cough, nasal obstruction and expectorations, gastrointestinal tract, such as diarrhea and nausea/vomiting, nervous system, specifically headache, dizziness/drowsiness and changes in smell/taste, and general feeling of sickness such as fever, myalgia, fatigue, and malaise were assessed.

Maternal and neonatal outcomes

COVID-19 associated maternal outcomes, namely need for inpatient treatment, extreme critical illness, invasive ventilation, indication for cesarean section or pregnancy termination, as well as specific neonatal outcomes, namely stillbirth, NICU admission, death, gestational age (weeks) at birth, preterm birth (delivery between >24 and <37 weeks of gestation), fetal growth restriction, birth weight percentiles, APGAR scores, congenital malformations and respiratory support, were evaluated.

Statistical analyses

The study compares categorical variables among different SARS-CoV-2 variants using absolute and relative frequencies, employing Chi-Square tests for statistical significance. Continuous variables are expressed as means and standard deviations for each variant group, with significance tested via univariate analysis of covariance. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated to further analyze symptom differences between Delta vs. Wild-type/Alpha and Omicron vs. Wild-type/Alpha. Logistic regression models were used to evaluate the impact of potential confounding factors, such as trimester at COVID-19 symptom onset or SARS-CoV-2 vaccination status, on observed differences in severe (e.g., dyspnea, fever) and mild symptoms (e.g., change in smell/taste, headache) between variants. Furthermore, logistic regression models were employed to investigate the association between symptoms and pregnancy outcomes, including ICU admission and preterm birth. Covariates considered SARS-CoV-2 variants, trimester at COVID-19 symptom onset, and SARS-CoV-2 vaccination status. Statistical analyses were performed using SPSS (version 28.01; IBM, Armonk, NY, USA) for Windows (Microsoft, Redmond, WA, USA). Missing values were handled by SPSS by default, potentially resulting in variations in sample sizes for analyses. Descriptive inferential statistics were applied, with significance set at $P < 0.05$.

Results

Demographics

A total of 8,541 data sets were obtained. Due to duplicates, missing data, or implausible entries, 508 cases were excluded. Additionally, 922 cases had less than an 80% probability of being assigned to a specific variant and were excluded. Out of the remaining 7,110 women with an ≥80% probability of a specific virus variant, 5,431 (76.39%) were symptomatic, 1,112 (15.6%) were asymptomatic, and data for 567 (8.0%) were missing. Among the 5431 pregnant women diagnosed with symptomatic SARS-CoV-2 infection and a probability of at least 80% for a specific virus variant, 1841 (33.9%) were attributed to the Wild-type/Alpha variant, 1171 (21.56%) to the Delta variant, and 2419 (44.5%) to the Omicron variant. Women infected with the Omicron variant were older compared to those infected with the Delta or Wild-type/Alpha variants. However, participants infected with the Delta or Omicron variants were more likely to smoke. The mean gestational age at the onset of COVID-19 symptoms increased throughout the pandemic (Wild-type/Alpha: 25.12 ± 10.90; Delta: 26.73 ± 9.15; Omicron: 28.9 ± 8.68 weeks) (Table 1).

General clinical symptoms

The occurrence of COVID-19 related respiratory symptoms exhibited significant shifts with the emergence of different variants (Table 2). While dyspnea prevalence was similar between Wild-type/Alpha and Delta variants (31.0% [531/1715] vs. 31.2% [346/1110], OR 1.01, 95% CI 0.86-1.19), Omicron infection significantly reduced the risk compared to Wild-type/Alpha (16.2% [371/2295] vs. 31.0% [531/1715], OR 0.43, 95% CI 0.37-0.50). Cough was more prevalent among women with Delta (79.9% [838/1049]) and Omicron (73.2% [1522/2080]) infections compared to Wild-type/Alpha (61.0% [1038/1702]). Similarly, nasal obstruction increased steadily over time from Wild-type/Alpha to Delta to Omicron (41.8% [697/1668] vs. 53.3% [498/935] vs. 62.4% [1203/1927]). Additionally, the risk of expectoration increased significantly from Wild-type/Alpha to Delta to Omicron dominance (9.9% [153/1552] vs. 15.5% [136/877] vs. 17.1% [302/1768]).

Table 1
Baseline and pregnancy characteristics of symptomatic study participants included in the study depending on the SARS-CoV-2 virus variant.

	Wild-type/Alpha $n = 1841$	Delta $n = 1171$	Omicron $n = 2419$	*P* value
Maternal characteristics				
Maternal age (years)[a]	31·08 ± 5·25	31·07 ± 5·48	31·60 ± 5·07	0·001
15-24	206/1838 (11·2)	142/1171 (12·1)	214/2400 (8·9)	0·03
25-34	1143/1838 (62·2)	715/1171 (61·1)	151372400 (63·0)	
35-49	489/1838 (26·6)	314/1171 (26·8)	673/2400 (28·0)	
Ethnic background				< 0·001
Europe	1189/1746 (68·1)	714/979 (72·9)	1652/2002 (82·5)	
Middle East	395/1746 (22·6)	190/979 (19·4)	239/2002 (11·9)	
Other	162/1746 (9·3)	75/979 (7·7)	111/2002 (11·5)	
Nulliparity	723/1828 (39·6)	429/1166 (36·8)	935/2398 (39·0)	0·30
Smoking (before pregnancy)	125/1735 (7·2)	131/970 (13·5)	278/2059 (13·5)	< 0·001
SARS-CoV-2 vaccination	4/1764 (0·2)	196/1089 (18·0)	1494/2297 (65·0)	< 0·001
Maternal comorbidities				
BMI > 30 (before pregnancy)	347/1682 (20·6)	215/1089 (19·7)	422/2289 (18·4)	0·22
Cardiovascular comorbidities	83/1814 (4·6)	40/1154 (3·5)	99/2373 (4·2)	0·34
Diabetes mellitus (preexisting)	20/1814 (1·1)	13/1154 (1·1)	28/2373 (1·2)	0·97
Pulmonary comorbidities	59/1814 (3·3)	33/1154 (2·9)	88/2373 (3·7)	0·40
Hematologic comorbidities	32/1814 (1·8)	26/1154 (2·3)	53/2372 (2·2)	0·51
Pregnancy characteristics				
Multiple gestation	49/1833 (2·7)	32/1162 (2·8)	74/2395 (3·1)	0·70
Gestational age (week) at onset of COVID-19 symptoms	25·12 ± 10·90	26·73 ± 9·15	28·9 ± 8·68	< 0·001
1st trimester	357/1841 (19·4)	121/1171 (10·3)	173/2419 (7·2)	< 0·001
2nd trimester	573/1841 (31·1)	438/1171 (37·4)	717/2419 (29·6)	
3rd trimester	911/1841 (49·5)	612/1171 (52·3)	1529/2419 (63·2)	

BMI, body mass index.
Data are shown as mean ± standard deviation or absolute/relative frequencies (percentage).
[a] Wild-type/Alpha: $n = 1839$, Delta: $n = 1171$; Omicron: $n = 2400$.

Table 2
Symptoms in pregnant patients with COVID-19 depending on the SARS-CoV-2 virus variant.

	Wild-type/Alpha	Delta	Omicron		Delta vs· Wild-type/Alpha		Omicron vs· Wild-type/ Alpha	
	$n = 1841$	$n = 1171$	$n = 2419$	*P* value	OR	95% CI	OR	95% CI
Respiratory tract								
Dyspnea	531/1715 (31·0)	346/1110 (31·2)	371/2295 (16·2)	< 0·001	1·01	0·86-1·19	0·43	0·37-0·50
Cough	1038/1702 (61·0)	838/1049 (79·9)	1522/2080 (73·2)	< 0·001	2·54	2·12-3·04	1·75	1·52-2·00
Nasal obstruction	697/1668 (41·8)	498/935 (53·3)	1203/1927 (62·4)	< 0·001	1·59	1·35-1·87	2·32	2·02-2·65
Expectorations	153/1552 (9·9)	136/877 (15·5)	302/1768 (17·1)	< 0·001	1·68	1·31-2·15	1·88	1·53-2·32
Gastrointestinal tract								
Diarrhea	139/1662 (8·4)	93/923 (10·1)	141/1791 (7·9)	0·14	1·23	0·92-1·61	0·94	0·73-1·20
Nausea/vomiting	205/1558 (13·2)	139/885 (15·7)	257/1779 (14·4)	0·21	1·23	0·97-1·55	1·11	0·92-1·36
Neurological symptoms								
Headache	707/1672 (42·3)	466/952 (48·9)	1058/1913 (55·3)	< 0·001	1·31	1·12-1·54	1·69	1·48-1·93
Dizziness/drowsiness	210/1559 (13·5)	145/875 (16·6)	260/1765 (14·7)	0·12	1·28	1·01-1·61	1·11	0·91-1·35
Changes in smell/taste	891/1680 (53·0)	510/939 (54·3)	446/1811 (24·6)	< 0·001	1·05	0·90-1·24	0·29	0·25-0·33
General feeling of sickness								
Fever	619/1692 (36·6)	444/994 (44·7)	746/1953 (38·2)	< 0·001	1·40	1·19-1·64	1·07	0·94-1·23
Myalgia	651/1671 (39·0)	445/941 (47·3)	964/1927 (50·0)	< 0·001	1·41	1·20-1·65	1·57	1·37-1·79
Fatigue	922/1678 (54·9)	562/942 (59·7)	1182/1927 (61·3)	< 0·001	1·21	1·03-1·42	1·30	1·14-1·49
Malaise	1030/1680 (61·3)	636/974 (65·3)	1133/1927 (58·8)	0·003	1·19	1·01-1·40	0·90	0·79-1·03

Data are shown as absolute/relative frequencies (percentage).

The odds of experiencing fever (44.7% [444/994] vs. 36.6% [619/1692], OR 1.4, 95% CI 1.19-1.61), myalgia (47.3% [445/941] vs. 39.0% [651/1671], OR 1.41, 95% CI 1.2-1.65), fatigue (59.7% [562/942] vs. 54.9% [922/1678], OR 1.21, 95% CI 1.03-1.42), or malaise (65.3% [636/974] vs. 61.3% [1030/1680], OR 1.19, 95% CI 1.01-1.4) were all higher in patients infected with the Delta variant compared to the Wild-type/Alpha variant. Similarly, myalgia (50.0% [964/192] vs. 39.0% [651/1671], OR 1.57, 95% CI 1.37-1.79) and fatigue (61.3% [1182/1927] vs. 54.9%, [922/1678] OR 1.30, 95% CI 1.14-1.49) were significantly increased in patients infected with the Omicron variant compared to the Wild-type/Alpha variant.

The likelihood of headaches increased in women infected with the Delta variant compared to those with the Wild-type/Alpha variant (48.9% [466/952] vs. 42.3% [707/1672], OR 1.31, 95% CI 1.12-1.54), with the highest occurrence noted for the Omicron variant (55.3% [1058/1913]). When restricted to women with the Wild-type/Alpha and the Delta variants, an increase in dizziness/drowsiness was observed (13.5% [210/1559] vs. 16.6% [145/875], OR 1.28, 95% CI 1.01-1.61).

The likelihood of smell/taste changes was comparable between Delta and Wild-type/Alpha variants (54.3% [510/939] vs. 53.0% [891/1680], OR 1.05, 95% CI 0.9-1.24). Conversely, Omicron infection significantly decreased occurrences compared to Wild-type/Alpha (24.6% [446/1811] vs. 53.0% [891/1680], OR 0.29, 95% CI 0.25-0.33).

In a multivariate analysis, we explored whether factors such as “trimester at COVID-19 symptom onset” or “SARS-CoV-2 vaccination” might obscure the observed differences in severe symptoms like “dyspnea” and “fever,” as well as mild symptoms such as “changes in smell/taste” and “headache” among the three variants, as shown in Table 3. None of the covariates were able to mitigate

Table 3
Association of selected COVID-19 symptoms and SARS-CoV-2 variant considering trimester of infection and vaccination status.

	Level	aOR	95% CI	*P* value
Dyspnea				
Delta	Wild-type/Alpha	1·03	0·87-1·22	0·76
Omicron	Wild-type/Alpha	0·45	0·37-0·55	< 0·001
2nd trimester[a]	1st trimester	1·18	0·94-1·47	0·16
3rd trimester[a]	1st trimester	1·22	0·99-1·51	0·06
SARS-CoV-2 vaccination	no vaccination	0·93	0·77-1·14	0·49
Fever				
Delta	Wild-type/Alpha	1·48	1·25-1·74	< 0·001
Omicron	Wild-type/Alpha	1·35	1·13-1·60	0·001
2nd trimester[a]	1st trimester	1·04	0·84-1·27	0·74
3rd trimester[a]	1st trimester	0·97	0·80-1·18	0·79
SARS-CoV-2 vaccination	no vaccination	0·69	0·59-0·82	< 0·001
Changes in smell/taste				
Delta	Wild-type/Alpha	1·09	0·92-1·29	0·35
Omicron	Wild-type/Alpha	0·28	0·23-0·34	< 0·001
2nd trimester[a]	1st trimester	0·77	0·63-0·95	0·02
3rd trimester[a]	1st trimester	0·59	0·49-0·73	< 0·001
SARS-CoV-2 vaccination	no vaccination	1·20	0·99-1·46	0·06
Headache				
Delta	Wild-type/Alpha	1·38	1·16-1·63	< 0·001
Omicron	Wild-type/Alpha	1·81	1·51-2·16	< 0·001
2nd trimester[a]	1st trimester	0·76	0·62-0·93	0·008
3rd trimester[a]	1st trimester	0·42	0·35-0·51	< 0·001
SARS-CoV-2 vaccination	no vaccination	1·13	0·96-1·34	0·15

[a] Trimester at onset of SARS-CoV-2 infection. aOR, adjusted Odds Ratio.

the significant influence of the virus variant on the discrepancy in the occurrence of typical symptoms.

Infection with the Omicron variant significantly decreased the risk of dyspnea compared to the Wild type/Alpha variant (adjusted OR [aOR] 0.45, 95% CI 0.37-0.55) irrespective of vaccination status or trimester of disease onset. Conversely, the likelihood of fever increased with Delta (aOR 1.48, 95% CI 1.25-1.74) and Omicron (aOR 1.34, 95% CI 1.13-1.6). Furthermore, Omicron was associated with a reduced likelihood of changes in smell or taste (aOR 0.28, 95% CI 0.23-0.34). The likelihood of headache was higher in Delta-infected individuals (aOR 1.38, 95% CI 1.16-1.63) and even greater in Omicron-infected individuals (aOR 1.81, 95% CI 1.51-2.16) compared to Wild type/Alpha variant infection. However, covariates exerted a partial influence. We observed that the later the trimester of COVID-19 onset, the less frequent were changes in smell/taste (3rd trimester; aOR 0.60, 95% CI 0.49-0.72) and headaches (aOR 0.42, 95% CI 0.37-0.51) compared to the first trimester. Vaccination reduced the risk of fever (aOR 0.69, 95% CI 0.59-0.82) but had no effect on dyspnea, headache, or changes in smell or taste.

COVID-19 associated adverse maternal outcomes

Transitioning from the Wild-type/Alpha to the Delta variant exacerbated adverse maternal outcomes associated with COVID-19 (Table 4). The proportions of COVID-19-related need for inpatient treatment (16.6% [299/1804] vs. 22.0% [249/1132]), pneumonia (6.0% [105/1762] vs. 10.7% [120/1125]), and ICU admission (4.9% [88/1799] vs. 8.0% [90/1128]) substantially increased. Moreover, there was at least a twofold increase in the risk for maternal mortality (0.2%(4/1799) vs. 0.4%(5/1123)), invasive ventilation (2.0% [36/1798] vs. 4.6% [52/1128]), extreme critical illness (2.7% [48/1798] vs. 5.3% [60/1126]), COVID-19-associated pregnancy termination (1.9% [31/1632] vs. 5.7% [58/1020]), and cesarean section (2.7% [44/1643] vs. 7.7% [79/1021]). Conversely, the emergence of the Omicron variant resulted in a decrease in COVID-19-related adverse maternal outcomes. Compared to infections with the Wild-type/Alpha or Delta variants, women infected with the Omicron variant exhibited the lowest risk of COVID-associated need for inpatient treatment (7.7% [180/2336]), pneumonia (0.6% [15/2322]), ICU admission (0.6% [15/2330]), mortality (0% [0/2330]), extreme critical illness (0.2% [5/2329]), and invasive ventilation (0.1% [2/2329]). Additionally, the proportion of women with COVID-19-associated reasons for pregnancy termination (0.2% [4/2061]) or cesarean section (0.6% [12/1989]) also decreased.

Neonatal outcomes

More women gave birth within 2 weeks after the onset of COVID-19 symptoms with a Delta variant infection (67.6% [698/1032]) and even more with an Omicron infection (77.1% [1645/2133]) compared to a Wild-type/Alpha infection (60.2% [997/1656]). The incidence of preterm birth (delivery between >24 and <37 weeks of gestation) (12.9% [212/1649] vs. 16.1% [163/1015]), fetal growth restriction (2.8% [48/1695] vs. 4.6% [49/1069]), 5 min APGAR score < 7 (3.6% [59/1639] vs. 6.5% [66/1014]), and need for respiratory support (8.1% [132/1621] vs. 10.7% [106/987]) all increased with a Delta infection compared to a Wild-type/Alpha infection. Conversely, infection with the Omicron variant resulted in preterm birth less frequently (10.6% [226/2130]) compared to both the Delta and the Wild-type/Alpha variants. The incidence of fetal growth restriction increased with both the Delta variant and the Omicron variants compared to the Wild-type/Alpha variant (2.8% [48/1695] vs. 4.6% [49/1069] vs. 4.2% [93/2199]). Furthermore, the incidence of a 5 min APGAR score < 7 was lowest among women with the Omicron variant compared to the other variants (3.6% [59/1639] vs. 6.5% [66/1014] vs. 2.3% [49/2122]). A similar trend was observed for the need for respiratory support, which was also lowest during the Omicron-dominant period of the pandemic (8.1% [132/1621] vs. 10.7% [106/987] vs. 5.4% [115/2103]). Gestational age at birth was lowest in the Delta period (37.6 weeks) and similar during the Wild-type/Alpha (38.2 weeks) and the Omicron variant dominant periods (38.4 weeks).

Subsequently, we investigated whether the presence of four symptoms—dyspnea, fever, changes in smell/taste, and headache—had an impact on maternal ICU admission and preterm birth, considered severe maternal and fetal outcome parameters (Table 5). The occurrence of severe symptoms dyspnea (aOR 20.25, 95% CI 12.83-31.97) and fever (aOR 5.84, 95% CI 4.01-8.51) emerged as strong predictors of maternal ICU admission, whereas the milder symptoms headache (aOR 1.37, 95% CI 0.98-1.92) and changes in smell/taste (aOR 0.38, 95% CI 0.26-0.55) held no predictive value. Similarly, dyspnea (aOR 1.51, 95% CI 1.24-1.85) and fever (aOR 1.34, 95% CI 1.11-1.62) were associated with an increased probability of preterm birth. Conversely, the occurrence of headache (aOR 0.83, 95% CI 0.68-1.01) did not contribute to an elevated risk, while changes in smell/taste (aOR 0.69, 95% CI 0.56-0.85) were associated with a lower risk of preterm birth.

Discussion

Using prospectively collected data from the CRONOS registry in Germany, we investigated the correlation between SARS-CoV-2 variants and clinical symptoms during pregnancy. Additionally, we examined the predictive value of these symptoms for adverse COVID-related maternal and neonatal outcomes. Infected with the Delta variant, we observed the highest risk for all investigated respiratory tract symptoms except dyspnea. Additionally, the risk of headache, dizziness, and drowsiness increased compared to Wild-type/Alpha variant infection. These findings mirror the more severe forms of COVID-19 seen in the general population [10,11].

Infections with the Omicron variant showed milder symptoms of COVID-19 compared to the Wild-type/Alpha or Delta variants. Pregnant women during the Omicron dominant period had the lowest risk of dyspnea and changes in smell/taste, but the highest

Table 4
Maternal and neonatal outcomes depending on the SARS-CoV-2 virus variant.

	Wild-type/Alpha $n = 1841$	**Delta** $n = 1171$	**Omicron** $n = 2419$	*P* value
Maternal outcomes				
COVID-19 associated need for inpatient treatment[a]	299/1804 (16·6)	249/1132 (22·0)	180/2336 (7·7)	< 0·001
Pneumonia	105/1762 (6·0)	120/1125 (10·7)	15/2322 (0·6)	< 0·001
ICU admission	88/1799 (4·9)	90/1128 (8·0)	15/2330 (0·6)	< 0·001
Mortality	4/1799 (0·2)	5/1123 (0·4)	0/2330 (0·0)	0·01
Extreme critical illness	48/1798 (2·7)	60/1126 (5·3)	5/2329 (0·2)	< 0·001
Invasive ventilation	36/1798 (2·0)	52/1128 (4·6)	2/2329 (0·1)	< 0·001
COVID-19 associated indication for cesarean section	44/1643 (2·7)	79/1021 (7·7)	12/1989 (0·6)	< 0·001
COVID-19 associated reason for pregnancy termination	31/1632 (1·9)	58/1020 (5·7)	4/2061 (0·2)	< 0·001
Neonatal outcomes				
Delivery within 2 weeks after onset of COVID-19 symptoms	997/1656 (60·2)	698/1032 (67·6)	1645/2133 (77·1)	< 0·001
Stillbirth[b]	16/1645 (1·0)	10/1008 (1·0)	7/2118 (0·3)	< 0·001
NICU admission	226/1621 (13·9)	171/987 (17·3)	238/2103 (11·3)	< 0·001
Neonatal death	4/1624 (0·2)	3/1002 (0·3)	7/2095 (0·3)	0·89
Gestational age (weeks) at birth	38·18 ± 2·97	37·57 ± 3·91	38·43 ± 2·55	< 0·001
Preterm birth[c]	212/1649 (12·9)	163/1015 (16·1)	226/2130 (10·6)	< 0·001
Fetal growth restriction	48/1695 (2·8)	49/1069 (4·6)	93/2199 (4·2)	0·03
Birth weight percentiles				0·25
<10th percentile	111/1401 (7·9)	93/947 (9·8)	205/2035 (10·1)	
10th to 90th percentiles	1161/1401 (82·9)	776/947 (81·9)	1658/2035 (81·5)	
>90th percentile	129/1401 (9·2)	78/947 (8·2)	172/2035 (8·5)	
5 min Apgar	9·32 ± 1·55	9·07 ± 1·94	9·51 ± 1·18	< 0·001
5 min Apgar < 7	59/1639 (3·6)	66/1014 (6·5)	49/2122 (2·3)	< 0·001
Congenital malformations	39/1641 (2·4)	32/999 (3·2)	40/2095 (1·9)	0·84
Respiratory support	132/1621 (8·1)	106/987 (10·7)	115/2103 (5·4)	0·04

Data are shown as absolute/relative frequencies (percentage) or mean ± SD.
ICU, intensive care unit; NICU, neonatal intensive care unit.
[a] Combined endpoint is composed of the following: pneumonia, ICU admission, mortality.
[b] Based on gestational age of SARS-CoV-2 infection >24 weeks of gestation.
[c] Based on delivery >24 and <37 weeks of gestation.

risk of respiratory symptoms like cough, nasal obstruction, and expectoration, as well as headaches, myalgia, and fatigue compared to the Wild-type/Alpha and Delta variant dominant periods. The data suggests COVID-19 transitioned from an illness primarily associated with cough and shortness of breath during the Delta variant dominance to include more severe respiratory and neurological symptoms and increased malaise. While Omicron presents as a less severe manifestation, it still involves a notable proportion of non-specific symptoms, significantly impacting the quality of life for pregnant women and potentially leading to hospitalization [12].

To further analyze the influence of additional factors, we conducted a multivariate analysis, confirming that each individual variant's impact persisted even after adjusting for the trimester of COVID-19 onset during pregnancy and vaccination status. Notably, the symptom profile remained consistent regardless of vaccination status; there were no discernible changes in symptoms between vaccinated and unvaccinated women. This is an extension of previous data showing that vaccination is associated with milder clinical presentations and reduces the risk of maternal hospitalization, preterm birth and NICU admission [5–7,13,14]. There are few studies on predictive factors for adverse outcomes in pregnant women. In a machine learning approach, we identified sFlt-1/PlGF and LDH as predictive parameters [15]. LDH values at admission were also shown by Arslan et al. to be an early and powerful predictor of severe infection in pregnant women with COVID-19 undergoing a cesarean section [16]. Other studies have revealed a correlation between positive pregnancy status and severe COVID-19, often associated with a cytokine storm, a term that was never clearly defined [17].

Consistent with findings from other studies, maternal morbidity, and adverse outcomes, including ICU admission and ventilation rates, peaked during the Delta-dominant period. Favre et al. in the COVI-Preg study documented elevated risks of hospitalization, ICU admission, and advanced oxygen requirements among 2055 pregnant women in France and Switzerland during the Delta variant period compared to the pre-Delta period [18]. Similarly, Vousden et al. identified an elevated risk of oxygen treatment, pneumonia, ICU admission, or maternal death in the UK during this period [19].

While Poisson et al. were unable to demonstrate a difference in pregnancy outcomes among various virus variants in a retrospective cohort study of 501 women in France, Iannaccone et al. found an increase in preterm birth and stillbirth rates during the Alpha and Delta periods in the CRONOS registry [5,20]. Similarly, a retrospective study of 192 pregnant women in Serbia reported the highest frequency of stillbirths during the Delta period [21].

With the emergence of the Omicron variant, currently available data indicates a decrease in the risk of adverse maternal outcomes associated with COVID-19. In the initial analysis of the CRONOS registry in 2022, involving around 2000 women, a significant 30% decrease in COVID-19 hospitalizations and a remarkable 90% reduction in ICU admissions were observed during the Omicron period compared to the Wild-type/Alpha period [12]. Similar findings were reported from studies in Scotland and Turkey, further suggesting a lower rate of ICU admissions during the Omicron period compared to the Delta period [4,3].

Our data reveals that maternal infections with the Delta variant were associated with heightened severity of maternal outcomes compared to the Wild-type/Alpha variant, paralleled by less favorable neonatal outcomes. Conversely, the Omicron variant showed improved neonatal outcomes consistent with existing data [4]. The

Table 5
Association of selected COVID-19 symptoms, maternal ICU admission or preterm birth and SARS-CoV-2 variant considering trimester of infection and vaccination status.

	Level	aOR	95% CI	*P* value
Maternal ICU admission				
Dyspnea	no	20·25	12·83-31·97	< 0·001
Delta	Wild-type/Alpha	1·66	1·18-2·35	0·004
Omicron	Wild-type/Alpha	0·31	0·16-0·59	< 0·001
2nd trimester[a]	1st trimester	5·28	1·87-14·92	0·002
3rd trimester[a]	1st trimester	8·18	2·96-22·61	< 0·001
SARS-CoV-2 vaccination	no vaccination	0·34	0·16-0·71	0·004
Maternal ICU admission				
Fever	no	5·84	4·01-8·51	< 0.001
Delta	Wild-type/Alpha	1·51	1·08-2·13	0·02
Omicron	Wild-type/Alpha	0·17	0·09-0·34	< 0·001
2nd trimester[a]	1st trimester	5·26	1·87-14·80	0·002
3rd trimester[a]	1st trimester	8·33	3·03-22·88	< 0·001
SARS-CoV-2 vaccination	no vaccination	0·40	0·19-0·86	0·02
Maternal ICU admission				
Changes in smell/taste	no	0·38	0·26-0·55	< 0·001
Delta	Wild-type/Alpha	1·53	1·06-2·20	0·02
Omicron	Wild-type/Alpha	0·12	0·05-0·26	< 0·001
2nd trimester[a]	1st trimester	4·03	1·42-11·43	0·009
3rd trimester[a]	1st trimester	6·49	2·36-17·85	< 0·001
SARS-CoV-2 vaccination	no vaccination	0·41	0·18-0·92	0·03
Maternal ICU admission				
Headache	yes	1·377	0·98-1·92	0·07
Delta	Wild-type/Alpha	1·51	1·06-2·15	0·022
Omicron	Wild-type/Alpha	0·15	0·07-0·32	< 0·001
2nd trimester[a]	1st trimester	4·71	1·67-13·28	0·003
3rd trimester[a]	1st trimester	8·29	3·02-22·78	< 0·001
SARS-CoV-2 vaccination	no vaccination	0·36	0·16-0·79	0·01
Preterm birth				
Dyspnea	no	1·51	1·24-1·85	< 0·001
Delta	Wild-type/Alpha	1·26	0·99-1·59	0·06
Omicron	Wild-type/Alpha	0·87	0·66-1·15	0·33
2nd trimester[a]	1st trimester	1·37	0·99-1·91	0·06
3rd trimester[a]	1st trimester	1·24	0·90-1·71	0·18
SARS-CoV-2 vaccination	no vaccination	0·88	0·68-1·14	0·32
Preterm birth				
Fever	no	1·34	1·11-1·62	0·003
Delta	Wild-type/Alpha	1·24	0·97-1·58	0·09
Omicron	Wild-type/Alpha	0·78	0·59-1·04	0·09
2nd trimester[a]	1st trimester	1·44	1·01-2·04	0·04
3rd trimester[a]	1st trimester	1·35	0·97-1·89	0·08
SARS-CoV-2 vaccination	no vaccination	0·86	0·65-1·14	0·28
Preterm birth				
Changes in smell/taste	no	0·69	0·56-0·85	< 0·001
Delta	Wild-type/Alpha	1·13	0·87-1·46	0·36
Omicron	Wild-type/Alpha	0·74	0·55-1·00	0·047
2nd trimester[a]	1st trimester	1·57	1·09-2·28	0·02
3rd trimester[a]	1st trimester	1·44	1·01-2·05	0·046
SARS-CoV-2 vaccination	no vaccination	0·82	0·61-1·09	0·18
Preterm birth				
Headache	no	0·83	0·68-1·01	0·06
Delta	Wild-type/Alpha	1·26	0·98-1·62	0·08
Omicron	Wild-type/Alpha	0·87	0·65-1·16	0·34
2nd trimester[a]	1st trimester	1·50	1·05-2·15	0·03
3rd trimester[a]	1st trimester	1·34	0·95-1·90	0·10
SARS-CoV-2 vaccination	no vaccination	0·81	0·61-1·07	0·14

[a] Trimester at onset of SARS-CoV-2 infection. aOR, adjusted Odds Ratio.

COVI-Preg study reported a decreasing proportion of NICU admissions and infants with an APGAR score < 7 over the pandemic [18]. Notably, the 1833 included neonates did not experience worse outcomes with maternal Delta variant infection, particularly noteworthy as the study focused exclusively on unvaccinated pregnant women [18]. However, a limited retrospective cohort study comparing the Wild-type and Delta periods demonstrated elevated rates of preterm birth and NICU admissions in pregnancies affected by a Delta variant infection [22]. In summary, our study provides additional evidence indicating that Delta variant infection poses increased risks not only for mothers but also heightened morbidity in children.

We identified a correlation between symptoms and maternal as well as neonatal outcomes. Serious symptoms such as dyspnea and fever significantly increased the risk of maternal ICU admission and likelihood of preterm birth, consistent with existing data on non-pregnant adults where dyspnea has been associated with increased mortality [23]. A recent study involving 221 SARS-CoV-2 infected mothers and their exposed fetuses documented a high incidence of respiratory distress in uninfected neonates, particularly when born to unvaccinated individuals (OR 3.06, 95% CI 1.08-10.21) [24]. In our cohort, vaccination reduced the risk of fever (aOR 0.69, 95% CI 0.59-0.82) but had no discernible impact on the occurrence of dyspnea, headache, or changes in smell or taste. While

vaccination did not act as a confounding factor for preterm birth, it did contribute to a decreased risk of maternal ICU admission. Conversely, milder symptoms such as changes in smell/taste and headache did not correlate with an elevated risk of ICU admission or preterm birth.

Independent of the virus variant and symptoms, other main risk factors for ICU admission and maternal mortality have already been identified for our and other cohorts, including gestational age, BMI, diabetes, and maternal age [12,25].

Our findings offer valuable insights for assessing the likelihood of severe disease progression in pregnant women with COVID symptoms and alleviating potential concerns. This study's strength lies in its prospective design, its substantial study population and in its multi-center approach. However, several limitations exist. Recruitment exclusively from hospitals in Germany and Austria may affect representativeness. Despite high detection rates due to national testing strategies until summer 2022, women with milder symptoms may not have been tested, potentially influencing findings. Women in the third trimester, having more medical appointments, are overrepresented compared to those in the first and second trimesters. Asymptomatic women were excluded from analysis. Higher gestational age at symptom onset in Omicron-infected women could be due to coincidental detection during delivery admission. The surge in Omicron infections and strain on healthcare systems may have led to incomplete inclusion, potentially affecting results. Nonetheless, symptoms associated with Omicron infection were generally milder regardless of timing during pregnancy.

The virus variant responsible for the infections in participating women was not individually sequenced. Instead, cases were categorized based on the predominant variant at the time of illness, using data from the German Robert-Koch-Institute, with a threshold of 80% for assigning a case to a specific variant. Cases occurring during transitional periods between dominant variants, unable to be allocated with at least 80% certainty, were excluded to minimize misclassification while avoiding excessive exclusions. Nonetheless, up to 20% of cases could theoretically be misclassified, potentially impacting results.

As the pandemic progressed and vaccination rates increased, the percentage of vaccinated women rose. Given that vaccination is associated with less severe outcomes, the risk linked to a variant for unvaccinated pregnant women may be underestimated.

Moreover, the percentage of women with prior infection history increased over time. Re-infection is also linked to a reduced risk of severe outcomes. Vaccination and reinfection may contribute to the milder course of infections during the Omicron variant dominance. However, certain symptoms like nasal obstruction, expectoration, myalgia, fatigue, and headaches occurred more frequently despite vaccination or reinfection.

Conclusions

Our study comprehensively examined clinical symptom changes among pregnant women with symptomatic SARS-CoV-2 infection across the COVID-19 pandemic's main phases. The results indicate that symptom profiles are primarily influenced by the virus variant, with additional nuances related to gestational week at infection (e.g., headache) and vaccination status (e.g., fever). Symptom profiles featuring dyspnea and fever are associated with more severe outcomes, including maternal ICU admission and preterm birth. Importantly, vaccination influences maternal outcomes and serves as a predictor of severe outcomes like ICU admission. These findings offer insights for personalized counseling, considering symptom presentation, and underscore the critical role of vaccination for pregnant women and those planning pregnancy. With ongoing virus evolution and new variants emerging, such as Eris and Pirola, continuous recording and correlating of symptoms with potential complications for pregnant women and their children are imperative.

Declarations of competing interest

All authors declare no conflict of interest.

Funding

This work was supported by Krumme-Stiftung, German Society of Perinatal Medicine, Federal State of Schleswig-Holstein.

Ethical approval

This research project was reviewed and approved by the Ethics Committee of the University of Schleswig-Holstein (UKSH) (AZ: D 451/20) and local Ethical Committees as appropriate.

Acknowledgments

The authors are very grateful to the participating pregnant women, the contributing institutions, and Corinna Fruth for assistance and coordination in the CRONOS study center. We especially thank the following local collaborators of the CRONOS study group:

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