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SARS-CoV-2: Implications for maternal-fetal-infant and perinatal mortality, morbidity, pregnancy outcomes and well-being

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SARS-CoV-2: Implications for maternal-fetal-infant and perinatal mortality, morbidity, pregnancy outcomes and well-being

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Editorial: SARS-CoV-2: implications for maternal-fetal-infant and perinatal mortality, morbidity, pregnancy outcomes and well-being

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Editorial on the Research Topic
SARS-CoV-2: implications for maternal-fetal-infant and perinatal mortality, morbidity, pregnancy outcomes and well-being

Introduction

On the fourth anniversary of the report of unusual pneumonia cases later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of Coronavirus Disease 2019 (COVID-19) (1), it is instructive to review what has been learned about the impact of this emerging global disease on the health and wellness of pregnant individuals, neonates, infants, and children. By the end of 2023, nearly 7 million COVID-19 deaths had been reported to the World Health Organization (WHO) (Figure 1) (2).

Maternal effects and adverse pregnancy outcomes

Pregnant persons who contract COVID-19 are at increased risk for morbidity, intensive care unit admission, mechanical ventilation, and mortality compared with nonpregnant women (3–5) and those with diabetes mellitus, hypertension, and cardiovascular disease face greater severity of infection and adverse outcomes (6). SARS-CoV-2 is a multisystem disorder with particular affinity for neurological, immune and cardiovascular systems (7). COVID-19 in pregnancy increases risk for hypertensive disorders (8, 9). A study in this edition reported increased incidence of maternal chronic hypertension during the pandemic that linked to higher neonatal intensive care unit (NICU) admissions (Jegatheesan et al.). Affected populations were largely publicly

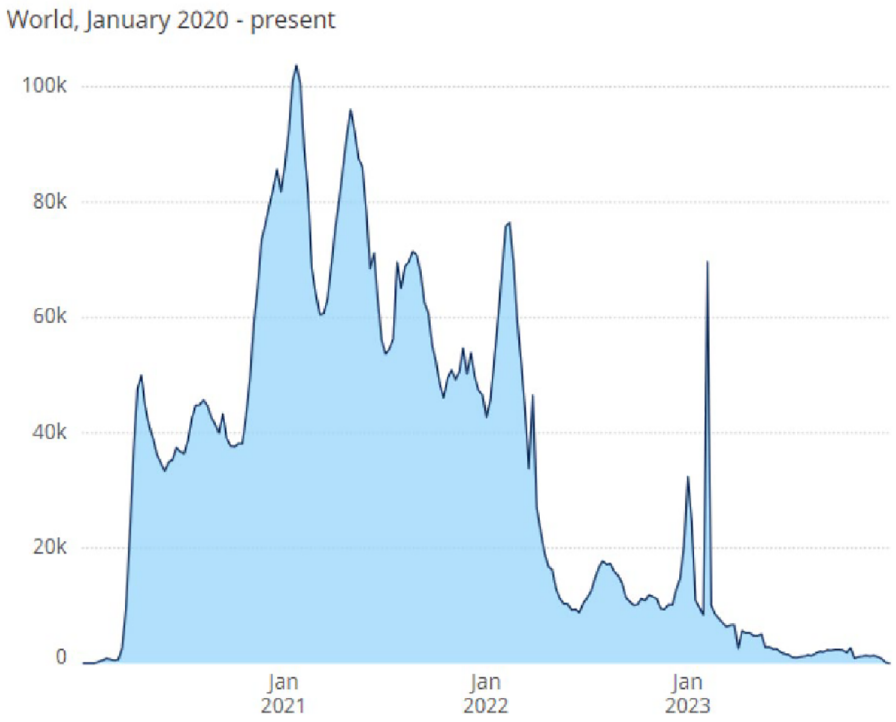

FIGURE 1
Total COVID-19 deaths reported to WHO (weekly). The World Health Organization (WHO) reports weekly deaths attributable to 3 COVID-19 infection worldwide (2).

insured individuals of color, accentuating existing obstetric health disparities. Hypertension in pregnancy predisposes to cardiovascular disease risk in the mother (10), intrauterine growth restriction, and programming of long-term cardiovascular (11) and neurodevelopmental health (12).

The impact of COVID-19 on preterm birth rates is complicated. Large cohort studies in international populations provided clear evidence that pregnant persons with symptomatic COVID-19 had significantly higher risk for preterm birth and NICU admission (3, 13, 14). Findings from temporal studies comparing rates before and after the onset of COVID-19 yielded mixed results likely reflecting other environmental influences. Lower preterm birth in multiple gestations in one German perinatal center was explained in part by restricted physical activity during lockdown (15). An analysis of 52 million births in 26 countries documented small decreases in preterm birth in the first 3 months of the pandemic lockdown, perhaps resulting from lower infection acquisition due to restricted social movement, better air quality from less traffic, and/or decrease in obstetric interventions for fetal wellbeing; only in Brazil was a concomitant increase in stillbirth noted (16). Several publications cited changing potency of circulating viral variants to explain fluctuating levels of infection acquisition and adverse perinatal outcomes over time (17–19). Others suggested that rising maternal immunity through prior infection or vaccination reduced infection incidence and complications over time (20, 21). The two studies included in this issue found no impact of COVID-19 on preterm birth rates (Rodriguez et al., Lorenzi et al.), which reinforces that infection risk is not randomly distributed in populations or over time and that combining data over several years may have diluted subtle time-sensitive effects.

Infant morbidity/mortality and long-term population health

Newborn COVID-19 is rarely the result of vertical transmission and more commonly is acquired through contact with family members, healthcare workers, and visitors. Most cases are asymptomatic or mildly symptomatic (22). Two descriptive studies in this edition report mild clinical courses for COVID-19 infected neonates in Chinese study populations (Yang et al., Dai et al.). Also in this compendium is a review of dermatologic manifestations of COVID that is particularly useful in infants in whom case identification may be complicated (Young).

More serious infant and childhood manifestations are rare, with a retrospective cohort study from China in this edition reporting a 1.8% incidence of seizures in children aged 6 months to 3 years (Xu et al.). We also include a case series describing four children with moderate-to-severe neonatal hepatitis following omicron infection which cautions that clinicians monitor liver function during recovery (Wang et al.).

Importantly, the provisional infant mortality rate for the United States rose 3% from 2021 to 2022, the first year-to-year

increase in two decades (23). The rise involved two leading causes of death: maternal complications and bacterial sepsis. While these data are preliminary and the underlying causes are likely to be multifactorial, COVID-19 may be a driver for the observed increase in infant mortality. The full impact of the pandemic on worldwide excess mortality has been estimated to exceed 300 deaths per 100,000 (24).

Long-term outcomes are being studied in children with fetal exposure to COVID-19. There is growing evidence that *in utero* exposure is associated with adverse neurodevelopmental sequelae, particularly in males (25, 26). Serious concerns reported in this edition involve a Brazilian birth cohort in which fetal COVID-19 exposure was associated with cerebral deep white matter changes suggesting zonal impairment of myelin content at 6 months adjusted age (Alves de Araujo et al.). These findings build on an established literature associating maternal infection, with fever and exaggerated immune response, with neurodevelopmental impairment including autism (27, 28).

Post-acute sequelae of COVID-19 infection (PASC) or Long COVID includes a broad set of persistent symptoms following infection. In a meta-analysis of 40 studies with 12,424 children, the pooled prevalence of Long COVID was 23.36% (29). A cohort study of 659,286 children with confirmed SARS-CoV-2 measured the incidence proportion of at least one feature of PASC was 41.9% in the COVID-positive group and 38.2% in those negative for COVID-19, for a difference of 3.7% (30). Increased rates were associated with acute illness severity, young age, and medical complexity. In adults, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), post-exertional malaise, memory loss and neurocognitive impairment are amongst the most common and debilitating Long COVID symptoms (31, 32). Systemic features of PASC often include viral persistence, chronic inflammation, hypercoagulability, and autonomic dysfunction (33, 34).

Mechanistic insights into disease

Cytokines are essential regulators of the immune response that mediate protective inflammation. Early studies suggest that some individuals respond to COVID-19 with exuberant proinflammatory cytokine proliferation, with interferon-gamma (IFN-γ), Interleukin-1 beta (IL-1β), and IL-6 most implicated, particularly in severe cases (35, 36). Two contributions in this edition evaluated cord blood for evidence of COVID-19 vaccine or infection-induced immune and inflammatory biomarker elevation. One reported higher cord blood levels of cortisol, critical to fetal and neonatal anti-inflammatory activities, in pregnancies exposed to SARS-CoV-2 but did not find elevation in acute phase reactants (Mendenhall et al.). The other found no increase in cord blood cytokine levels (Jain et al.). Neither finding was unexpected, as cytokines have relatively short lives, and both studies had lags between maternal infection and sample collection.

Underlying molecular mechanisms have been hypothesized in adult PASC. Mitochondrial dysfunction, involving impaired cellular energy production with redox imbalance and oxidative stress, has been implicated in the etiology of Long COVID (37) and the efficacy of coenzyme Q10 (CoQ10) supplementation is being investigated as a therapeutic strategy (38). Reduction in serotonin levels through viral and immunological processes in PASC appears to impair vagal nerve, hippocampal responses and memory and targeted interventions are under investigation (39). An elegant longitudinal cohort study explored the pathophysiology of Long-COVID post-exertional malaise and found that exercise caused immediate skeletal muscle alterations, including reduction in mitochondrial enzyme activity, increased accumulation of amyloid-containing deposits, blunted T-cell response, and severe tissue damage (40). The implications for all these findings in children are unclear but profoundly concerning.

Implications for health care services

Perinatal care practices evolved rapidly during lockdown in response to broad concerns for patient and provider safety Most face-to-face visits were replaced by remote monitoring and telehealth. Investigators are evaluating the adequacy of these health service modifications retrospectively. Three studies in this edition addressed the issue, with reassuring findings. One identified a slight delay in the timing of mid-pregnancy anatomy ultrasound scans during the pandemic that was unlikely to be clinically significant (Handley et al.). Another reported an increase in NICU admissions for hypoxic-ischemic encephalopathy (HIE) evaluation related to maternal hypertension but found no difference in HIE diagnosis or treatment (Song et al.). A final study demonstrated that there was no change in NICU discharge orders for maternal milk, though insured mothers were twice as likely to be providing milk perhaps due to the benefits of telework options not available to uninsured individuals (Boudreau et al.).

Conclusion

This edition of *Frontiers in Pediatrics* adds to the existing SARS-CoV-2 literature in important ways. While serious pregnancy adverse outcomes appear to be attenuating due to preventive and treatment measures, maternal infection may induce cardiovascular and immune changes with profound implications for the mother and fetus. *In utero* exposure may lead to a form of Long COVID that induces brain changes and neurodevelopmental consequences. Evidence continues to reassure that most neonatal and pediatric COVID-19 infections are mild, but clinicians must remain vigilant for rare more serious manifestations and the potential for Long COVID. Investigation of PASC and its underlying pathophysiology and molecular mechanisms in children is a high priority, as is the impact of telehealth on pregnant individuals, infants, and children in the endemic stage of COVID-19. Vaccination strategies must creatively target pregnant persons and infants 6 months of age and older (41, 42). Finally, given the

disproportionate impact of the pandemic on underrepresented communities already predisposed to excess perinatal morbidity and mortality, health officials must re-focus resources to optimize perinatal care quality through attention to the social determinates that place these populations at unacceptably enhanced risk.

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Conflict of interest

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Changes in prenatal testing during the COVID-19 pandemic

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Objective: The coronavirus disease 2019 (COVID-19) pandemic disrupted healthcare delivery, including prenatal care. The study objective was to assess if timing of routine prenatal testing changed during the COVID-19 pandemic.

Methods: Retrospective observational cohort study using claims data from a regional insurer (Highmark) and electronic health record data from two academic health systems (Penn Medicine and Yale New Haven) to compare prenatal testing timing in the pre-pandemic (03/10/2018–12/31/2018 and 03/10/2019–12/31/2019) and early COVID-19 pandemic (03/10/2020–12/31/2020) periods. Primary outcomes were second trimester fetal anatomy ultrasounds and gestational diabetes (GDM) testing. A secondary analysis examined first trimester ultrasounds.

Results: The three datasets included 31,474 pregnant patients. Mean gestational age for second trimester anatomy ultrasounds increased from the pre-pandemic to COVID-19 period (Highmark 19.4 vs. 19.6 weeks; Penn: 20.1 vs. 20.4 weeks; Yale: 18.8 vs. 19.2 weeks, all $p < 0.001$). There was a detectable decrease in the proportion of patients who completed the anatomy survey <20 weeks' gestation across datasets, which did not persist at <23 weeks' gestation. There were no consistent changes in timing of GDM screening. There were significant reductions in the proportion of patients with first trimester ultrasounds in the academic institutions (Penn: 57.7% vs. 40.6% and Yale: 78.7% vs. 65.5%, both $p < 0.001$) but not Highmark. Findings were similar with multivariable adjustment.

Conclusion: While some prenatal testing happened later in pregnancy during the pandemic, pregnant patients continued to receive appropriately timed testing. Despite disruptions in care delivery, prenatal screening remained a priority for patients and providers during the COVID-19 pandemic.

KEYWORDS

pregnancy, prenatal care, ultrasound, glucose tolerance test, gestational diabetes, access to care, COVID-19

Introduction

The coronavirus disease 2019 (COVID-19) pandemic created many disruptions in healthcare delivery, including obstetric care. Changes to obstetric care delivery were made quickly to decrease the risk of virus transmission across inpatient and outpatient settings (1, 2). Health systems and clinics responded by transitioning to or increasing virtual visits and adopting reduced visit schedules (3, 4). However, some aspects of prenatal care are not amenable to virtual care encounters. Essential services, such as the obstetric ultrasound to assess fetal anatomy and gestational diabetes screening, require in-person interactions (5, 6). The ability of health systems to provide, and pregnant patients to access these essential, in-person obstetric services in a timely manner during the COVID-19 pandemic is unclear.

To date, much of the literature regarding restructuring prenatal care in the setting of the COVID-19 pandemic has focused on telehealth visits and tailoring prenatal care schedules based on a pregnant patient's risk profile (7, 8). Studies have reported efforts to align in-person visits with essential obstetric testing, yet the frequency with which such testing was completed during the height of the pandemic is rarely described (3). There are also reports of combining ultrasound-based tests (e.g., first trimester dating ultrasound with an ultrasound to measure nuchal translucency) and examining completion of third trimester testing for HIV, syphilis, and routine urine collection as a marker of the adequacy of prenatal care (2, 9). Yet, despite the importance of second trimester testing in the ongoing management of a pregnancy and associated implications for the infant, from identification of birth defects to glucose monitoring after birth, the frequency and timing of such testing during the pandemic remains unknown.

The objective of this study was to assess if the timing of essential prenatal testing changed between the pre-pandemic and the early COVID-19 pandemic periods. We examined two second trimester services as primary outcomes the timing of (1) ultrasound for fetal anatomy and (2) gestational diabetes screening with a glucose tolerance test (GTT) or glucose challenge test (GCT). We examined receipt of first trimester ultrasound as a secondary outcome. Given the disruption and strain the COVID-19 pandemic created in the health care system, we hypothesized that routine screening would happen later in pregnancy during the COVID-19 pandemic.

Methods

Study design and population

This was a retrospective observational cohort study using claims data from an insurer in the MidAtlantic and electronic health record (EHR) data from two academic health systems to compare prenatal screening during the COVID-19 pandemic (03/10/2020–12/31/2020) with the pre-pandemic period (matched months in the two years prior; 03/10/2018–12/31/2018 and 03/10/2019–12/31/2019). This study was approved by the Children's Hospital of Philadelphia, University of Pennsylvania, and Yale University Institutional Review Boards.

Given the geographic, socioeconomic, and racial and ethnic differences in SARS-CoV-2 infection, hospitalizations, and deaths, analyses utilized data from three different and complementary sources to increase study generalizability (10–13). Insurer data came from Highmark, an independent licensee of the Blue Cross Blue Shield Association, that provided insurance coverage to people living in all of Delaware, southwestern Ohio (one county), across Pennsylvania (63 of 67 counties), and all of West Virginia during the study period. These data have geographic variation across metropolitan and non-metropolitan areas. The two health systems studied were Penn Medicine and Yale New Haven Hospital. The Penn Medicine health system serves the greater Philadelphia area, which spans southeastern Pennsylvania and central New Jersey, a major metropolitan region with racial, ethnic, and socioeconomic diversity. The Yale New Haven Health system provides care for the smaller metropolitan center of New Haven and the surrounding areas of Connecticut whose population composition is different than that in Philadelphia.

Pregnant patients included in the primary cohort, which was created to examine primary outcomes (second trimester testing), met al.l three of the following inclusion criteria: (1) <14 weeks' gestation by 03/10/2020 (last menstrual period 12/04/2019–3/9/2020); (2) gave birth at ≥20 weeks' gestation by 12/31/2020; and (3) singleton pregnancies. We used an analytic dataset from Highmark that required ZIP code to be non-missing. In order to capture appropriate prenatal care, further inclusion criteria depended on the data source. In those insured by Highmark, patients had to be enrolled in a plan by before 14 weeks' gestation. Patients at Penn Medicine and Yale New Haven Health systems had to have initiated prenatal care, either in-person or *via* telemedicine, before 28 weeks' gestation. The analytic dataset was checked to ensure that no pregnant patients were in both the Highmark and Penn Medicine data. A secondary cohort of pregnant patients, which was created to examine receipt of first trimester ultrasound, included pregnant patients who were <5 weeks' gestation by 03/10/2020 (last menstrual period 02/02/2020–03/09/2020), and met the same birth and prenatal care initiation criteria as the primary cohort.

Study outcomes

The primary outcomes were the timing of essential second trimester testing: (1) ultrasound to assess fetal anatomy (e.g.,

"anatomy scan", "full fetal survey") and (2) glucose tolerance testing (GTT) or glucose challenge testing (GCT) to screen for gestational diabetes. The second trimester of pregnancy included the period from 14 weeks and 0 days to 27 weeks and 6 days. Timing was assessed by the number of completed weeks' gestation. In addition to timing, the proportion of pregnant patients completing testing before 20 weeks' given potential implications for pregnancy management and by the recommended time point before 23 weeks' gestation for second trimester ultrasound and before 29 weeks' gestation for GTT/GCT was assessed.

The second trimester ultrasound to assess fetal anatomy was identified using current procedural terminology (CPT) codes 76805, 76810, 76811, 76812, 76813, 76815, and 76816 in the Highmark data, EHR procedure names "Ultrasound complete" and "US Preg 2nd/3rd tri" occurring at ≥14 weeks' gestation in the Penn Medicine data, and in the Yale New Haven data the aforementioned CPT codes with the addition of 76801 and 76802 for ultrasounds specified as "complete". If pregnant patients had more than one ultrasound to fully assess fetal anatomy, the first ultrasound to assess fetal anatomy was used to examine timing. The identification of GTT/GCT screening utilized CPT codes 82950, 82951, and 82952 in the Highmark data, EHR procedure names "1 h glucose gestational 1 h", "2 h glucose tolerance - 2 h", "2 h glucose tolerance 1 h", "2 h glucose tolerance fasting", "3 h glucose gestational 1 h", "3 h glucose gestational 2 h", "3 h glucose gestational 3 h", "3 h glucose gestational fasting", "Fasting glucose in glucose tolerance", "Glucose tolerance test,$gestational,4spec(100 g)", and "Glucose, gestational screen (50 g)-140 cutoff" in the Penn Medicine data, and all previously listed 1 and 3 h EHR procedure names in the Yale New Haven data. This definition considered the first GTT/GCT completed during the second trimester and did not differentiate between one-hour GCT or, two- or three-hour GTT.

The secondary outcome was receipt of first trimester ultrasound, which is routinely used to confirm an intrauterine pregnancy and provide an assessment of gestational age. This was defined as the first ultrasound of any type in the three data sources. The proportion of patients who completed a first trimester ultrasound before 14 weeks' gestation (when dating of a pregnancy is most accurate) was also examined.

Study variables

Pregnant patient and area-level sociodemographic characteristics as well as pre-existing and pregnancy-associated conditions were assessed, given associations with disparities related to COVID-19 and potential risk factors for increased prenatal testing. These characteristics included age (<20, 20–<25, 25–<30, 30–<35, and ≥34 years) (14), race/ethnicity (examined as Asian, Hispanic, Non-Hispanic Black, Non-Hispanic White, and Another, Unknown or Missing), insurance type (private or public) (15), pregnant patient ZIP code of residence, nulliparity, smoking during pregnancy [defined in Highmark data using International Classification of Diseases (ICD-10) code O993 and current smoker, former smoker, or never smoker in the EHR], obesity (identified in the Highmark data using ICD-10 codes E660–E662, E664–E669, Z683, Z684, and O9921 and a pre-pregnancy body mass index ≥30 in the EHR data), pre-existing hypertension (defined in the Yale New Haven data with ICD-10 codes I10–I16 or O10 and in the Penn data as these ICD-10 codes on two or more occurrences at least 30 days apart), hypertensive disorders of pregnancy, including gestational hypertension (defined in the Yale data with ICD-10 codes O12 and O13 and in the Penn data as these ICD-10 codes on two or more occurrences at least one day apart), preeclampsia (defined in the Yale data with ICD-10 codes O11 and O14 and in the Penn data as these ICD-10 codes on two or more occurrences at least one day apart), Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) (defined using ICD-10 code O142), and eclampsia (defined using ICD-10 code O15), pre-existing diabetes (defined in the Yale data as ICD-10 codes E08-E11, E13, O240, O241, and O243 and in the Penn data these ICD-10 codes on two or more occurrences at least 30 days apart) (16), gestational diabetes (defined in the Yale data as ICD-10 code O244 and in the Penn data as this ICD-10 code on two or more occurrences at least one day apart) (17), preterm birth (defined as birth <37 weeks' gestation), and SARS-CoV-2 positivity during pregnancy. Race/ethnicity and nulliparity variables were not available in the insurer data. Patient ZIP code was not available in the Yale EHR data.

Statistical analysis

Characteristics of patients across the three datasets were reviewed. Within each data source, bivariate analyses were used to compare pregnant patient sociodemographic characteristics and medical conditions in the pre-pandemic and the early COVID-19 pandemic periods. The timing of second trimester ultrasound to fully assess fetal anatomy, GTT/GCT, and initial first trimester ultrasound was similarly compared between periods. Bivariate tests of association were performed using χ^2 or Fisher exact test as appropriate for categorical measures, and *t*-test or Wilcoxon for continuous measures. Multivariable logistic regression models were used to assess changes in testing timing between the two periods. Specifically, changes in second trimester ultrasound to assess fetal anatomy before 20 and 23 weeks' gestation, GTT/GCT before 29 weeks' gestation, and the receipt of a first trimester United States were assessed. Model adjustment included the following variables: maternal age, insurance type, obesity, smoking, pre-existing hypertension and pre-gestational diabetes. Pre-gestational diabetes was not included in models

assessing GTT/GCT timing. Analyses were completed using SAS 9.4, Cary, NC.

Results

Across the three data sources there were 31,474 pregnant patients included. Of those, 22,167 (70.4%) were patients from the Highmark cohort, 5,724 (18.2%) from the Penn Medicine health system, and 3,583 (11.4%) from the Yale New Haven health system. Pregnant patient sociodemographic characteristics and medical conditions are reported in Table 1. Pregnant patients in the Highmark data were primarily privately insured (91.8%), the plurality of pregnant patients in the Penn Medicine data were non-Hispanic Black (41.3%), and the rates of smoking during pregnancy (7.3%) and pre-existing hypertension (10.1%) were higher in the pregnant patients from Yale New Haven. Patient characteristics between the pre-pandemic and early COVID-19 pandemic periods were compared within each dataset (Supplementary Table S1). There were no consistent differences in patient characteristics between periods across the datasets.

The mean week of gestation for the initial second anatomy scan was significantly later in the COVID-19 period across all three datasets (Highmark: pre-pandemic 19.4 weeks vs. COVID-19 19.6 weeks $p < 0.001$; Penn Medicine: pre-pandemic 20.1 weeks vs. COVID-19 20.4 weeks $p < 0.001$; Yale New Haven: pre-pandemic 18.8 weeks vs. COVID-19 19.2 weeks $p < 0.001$). Figure 1 (panel A) illustrates the distribution of timing for completion of a second trimester ultrasound for fetal anatomy. The proportion of patients who completed second trimester ultrasound testing <20 weeks during the COVID-19 pandemic period was lower in all three datasets (Highmark: pre-pandemic 70.3% vs. COVID-19 64.2% $p < 0.001$; Penn Medicine: pre-pandemic 21.5% vs. COVID-19 15.9% $p < 0.001$; Yale New Haven: pre-pandemic 82.5% vs. COVID-19 63.8% $p < 0.001$). In the adjusted models, the odds of a second trimester ultrasound occurring ≥20 weeks' gestation in the COVID-19 period was significantly higher in all three datasets (Table 2). By 23 weeks' gestation, the proportion of pregnant patients who completed second trimester ultrasound screening had increased with no detectable difference in rates between pre-pandemic and COVID-19 periods across data sources (Highmark: pre-pandemic: 96.5% vs. COVID-19 96.6% $p = 0.95$, Penn Medicine: pre-pandemic: 95.1% vs. COVID-19 93.9% $p = 0.08$, Yale New Haven: pre-pandemic: 96.7% vs. COVID-19 95.8% $p = 0.21$), findings which were consistent in the adjusted analysis (Table 2).

The mean week of gestation for which gestational diabetes testing was completed was similar between periods in the Highmark cohort and earlier in the academic institutions (Highmark: pre-pandemic 25.1 weeks vs. COVID-19 24.9 weeks $p = 0.1$; Penn Medicine: pre-pandemic 27.0 weeks vs. COVID-19 26.4 weeks $p < 0.001$; Yale New Haven: pre-pandemic 24.2 weeks vs. COVID-19 23.6 weeks $p = 0.01$). The distribution of timing of completion of gestational diabetes testing by gestation age week is shown in Figure 1 (panel B), for which there were no statistically significant changes in completion of timing before 29 weeks' gestation in the Highmark and Penn Medicine data (Highmark: pre-pandemic

TABLE 1 Patient characteristics in each of the three data sources.

Data source	Highmark	Penn Medicine	Yale New Haven
Total patients (n)	22,167	5,724	3,583
Birth year			
2018	7,954 (35.9%)	1,915 (33.5%)	1,227 (34.2%)
2019	7,404 (33.4%)	1,957 (34.2%)	1,192 (33.3%)
2020	6,809 (30.7%)	1,852 (32.4%)	1,164 (32.5%)
Sociodemographic characteristics			
Age (years)			
<20	595 (2.7%)	106 (1.9%)	84 (2.3%)
20–<25	3,340 (15.1%)	674 (11.8%)	398 (11.1%)
25–<30	6,501 (29.3%)	1,278 (22.3%)	864 (24.1%)
30–<35	7,462 (33.7%)	2,071 (36.2%)	1,304 (36.4%)
≥35	4,269 (19.3%)	1,595 (27.8%)	933 (26.0%)
Race and Ethnicity	Unavailable		
Hispanic	Unavailable	422 (7.4%)	775 (21.6%)
Non-Hispanic Asian	Unavailable	441 (7.7%)	199 (5.6%)
Non-Hispanic Black	Unavailable	2,363 (41.3%)	632 (17.6%)
Non-Hispanic White	Unavailable	2,220 (38.8%)	1,868 (52.1%)
Another/Unknown/Missing	Unavailable	278 (4.9%)	109 (3.0%)
Private Insurance	20,351 (91.8%)	3,488 (60.9%)	2,179 (60.8%)
Health characteristics			
Nulliparous	Unavailable	2,595 (45.3%)	1,484 (41.4%)
Smoked during pregnancy	1,028 (4.6%)	174 (3.0%)	263 (7.3%)
Obesity (BMI ≥30 kg/m^2)	4,929 (22.2%)	1,544 (27.0%)	1,014 (28.3%)
Pre-existing HTN	928 (4.2%)	332 (5.8%)	363 (10.1%)
Any HDP	2,628 (12.1%)	1,147 (20.0%)	742 (20.7%)
Gestational HTN	1,512 (6.8%)	741 (13.0%)	442 (12.3%)
Preeclampsia	964 (4.4%)	390 (6.8%)	269 (7.5%)
HELLP	64 (0.3%)	13 (0.2%)	14 (0.4%)
Eclampsia	88 (0.4%)	3 (0.1%)	17 (0.5%)
Preexisting diabetes	296 (1.3%)	129 (2.3%)	79 (2.3%)
Gestational diabetes	1,872 (8.4%)	424 (7.4%)	295 (8.6%)
Preterm birth (<37 weeks' gestation)	1,893 (8.5%)	502 (8.8%)	274 (7.7%)

BMI, body mass index; HTN, hypertension; HDP, hypertensive disorder of pregnancy; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets. Hypertensive disorder of pregnancy includes gestational hypertension, preeclampsia, HELLP, and eclampsia.

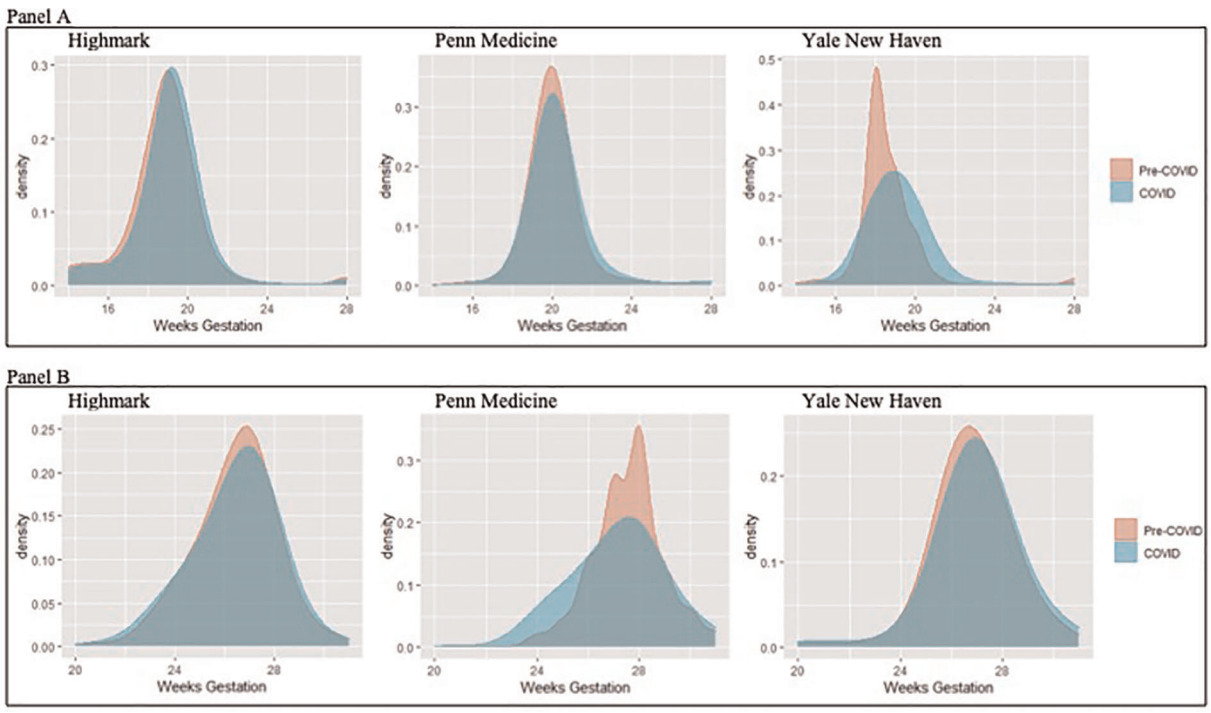

FIGURE 1
Distribution of completion of second trimester testing with an ultrasound to assess fetal anatomy (panel A) and gestational diabetes (panel B) across the three data sources.

TABLE 2 Unadjusted and adjusted odds of second trimester prenatal testing timing during the COVID-19 pandemic period.

Prenatal test	Highmark		Penn Medicine		Yale New Haven	
	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
First 2nd trimester fetal anatomy ultrasound ≥20 weeks	1.32 (1.24, 1.41)	1.33 (1.25, 1.41)	1.46 (1.25, 1.70)	1.46 (1.25, 1.71)	2.68 (2.28–3.14)	2.70 (2.29–3.17)
First 2nd trimester fetal anatomy ultrasound ≥23 weeks	0.98 (0.84, 1.15)	1.04 (0.89, 1.22)	1.27 (0.99, 1.64)	1.27 (0.98, 1.65)	1.27 (0.88–1.83)	1.30 (0.89–1.88)
First GCT/GTT ≥29 weeks	0.92 (0.82, 1.04)	1.00 (0.88, 1.12)	0.93 (0.80, 1.07)	0.91 (0.79, 1.06)	1.31 (1.03–1.66)	1.38 (1.08–1.76)

All models reference the pre-pandemic period. GCT/GTT models reference testing between 20 and 29 completed weeks' gestation.

90.9% vs. COVID-19 91.5% $p = 0.21$, Penn Medicine: pre-pandemic 75.5% vs. COVID-19 76.5% $p = 0.45$) and a decrease in the proportion of testing completed before 29 weeks' gestation in the Yale New Haven data (pre-pandemic 87.8% vs. COVID-19 84.7% $p = 0.03$). These results were consistent in the adjusted models (Table 2).

Across the three data sources there were a total of 6,310 pregnant patients in the secondary cohort who were <5 weeks' gestation by 03/10/2020 for which the secondary outcome of first trimester ultrasound was examined. The distribution of timing for the initial ultrasound in the first trimester is shown in Figure 2. The proportion of pregnant patients who completed a first trimester ultrasound (before 14 weeks' gestation) was unchanged during the COVID-19 pandemic period for patients captured in the Highmark data (pre-pandemic 82.4% vs. 83.8%, $p = 0.63$), but decreased significantly among patients seen in the Penn Medicine and Yale New Haven health systems (Penn Medicine pre-pandemic 58.7% vs. COVID-19 41.0%, $p = <0.001$; Yale New Haven 78.8% vs. COVID-19 66.8%, $p = <0.001$). This finding in the academic institutions persisted in adjusted analyses, as the COVID-19 period was associated with higher odds of not completing a first trimester ultrasound (Penn Medicine: adjusted odds [aOR] 2.11, 95% confidence interval [CI] 1.74, 2.56, Yale New Haven: aOR 1.93, 95% CI 1.49, 2.51).

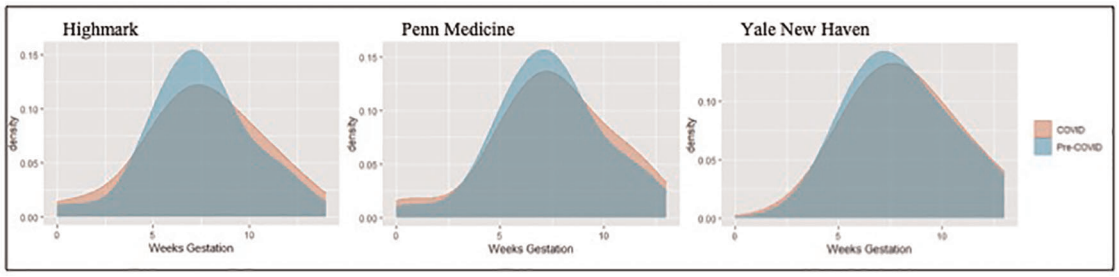

FIGURE 2
Distribution of completion of first trimester ultrasound across the three data sources.

Discussion

Although the average time at which second trimester ultrasounds occurred during the early phase of the COVID-19 pandemic was later in pregnancy, overall patients continued to receive appropriate routine prenatal second trimester ultrasounds and gestational diabetes testing. However, in both academic institutions the rate of receipt and adjusted odds of a first trimester ultrasound was significantly lower during the COVID-19 period. While our data demonstrate that prenatal testing during the second trimester in the COVID-19 period continued to meet guidelines from professional organizations, first trimester, in-person services may have been deprioritized.

The Guidelines for Perinatal Care recommend completion of an ultrasound to assess fetal anatomy between 18 and 22 weeks' gestation (18). While our data demonstrate there was no difference in the proportion of pregnant patients who completed this testing in the recommended time frame (before 23 weeks' gestation), we did appreciate a shift in the mean gestational week during which this testing occurred and the proportion of scans completed before 20 weeks' gestation. The reason for this shift is likely multifactorial. First, prior to the pandemic, there were baseline practice differences across the three patient groups, with patients in the Yale New Haven system often receiving a second trimester ultrasound for fetal anatomy earlier in gestation than the other cohorts. Second, the shift in timing seen across the three datasets likely reflects systemic changes. For example, practices shifted scans to later in gestation to avoid incomplete image acquisition which requires additional in-person encounters increasing the risk of COVID-19 exposure. However, while screening was still completed as recommended, the shift in timing may have implications for pregnancies in which abnormal fetal anatomy is diagnosed. The detection of severe and potentially life-limiting congenital anomalies may influence a patient's decision to end a pregnancy which is often very time sensitive. Furthermore, associated diagnoses made during the second trimester may affect ongoing monitoring of complicated pregnancies and at-risk fetuses identified during second trimester ultrasound testing.

Our data regarding glucose tolerance testing was not consistent across the data sources, with a detectable shift only noted in the Yale New Haven data. This shift may reflect changes in coordination of in-person appointments and testing, which have been described in the literature at other academic institutions who were working to streamline appointments and decrease the number of contacts with the healthcare system. However, the overall timely completion of gestational diabetes testing likely reflects the dedication of providers and patients to ensure the timeliness of this testing, given the downstream effects on blood sugar management *via* dietary changes and medication initiation, which has implications for maternal, fetal, and neonatal wellbeing.

One of the more surprising findings was the change in receipt of a first trimester ultrasound, which was a prominent finding in the two academic health systems studied, but not in the Highmark data. It is important to consider potentially contributing factors. One factor may be the differences in sociodemographic characteristics between patients captured in the different data sources, specifically insurance type. A much higher percentage of the Highmark patients were privately insured, a characteristic associated with utilization of obstetric care and early initiation of prenatal care (19, 20). Another explanation is that the capture of first trimester ultrasounds is more complete in the insurer data as it reflects billable services outside of a single health system. In contrast, it is plausible that patients in the Penn Medicine or Yale New Haven cohorts were more likely to have their first trimester ultrasounds completed outside of these respective health systems, especially during the peak of the pandemic if patients perceived the burden of COVID-19 to be higher in tertiary health systems. However, the low rates of first trimester ultrasounds are concerning. First trimester ultrasounds are standardly used in conjunction with the last menstrual period to determine the gestational age of a pregnancy. Without an accurate last menstrual period or first trimester ultrasound, pregnancy dating is less accurate, which can have

ramifications on pregnant patients and their infants both at the limits of viability as well as management of pregnancies that surpass their estimated due date. First trimester ultrasounds allow for the confirmation of an intrauterine pregnancy, identification of multiple gestation pregnancies, and diagnosis of cesarean scar pregnancies and other abnormalities or disorders that may affect the health of the pregnant patient, viability of the pregnancy, and associated monitoring. A first trimester ultrasound is also often a component of aneuploidy screening and may facilitate early diagnosis of severe anomalies (e.g., acrania). Timely diagnosis of severe pregnancy related abnormalities or complications and congenital anomalies during the first trimester is particularly relevant and may be time-sensitive given evolving access to abortion services in the United States.

This study has limitations. The three datasets did not have all the same variables available. For example, race and ethnicity and nulliparity were not available in the Highmark data. Similarly, not all variables were captured in the same way across the three datasets (i.e., use of CPT codes vs. EHR procedure names). Though we worked to harmonize the data as best as possible, these differences may contribute to variability across cohorts (i.e., rates of hypertension). We could not determine the reason for first trimester ultrasounds and could not differentiate between viability and dating ultrasounds. While changes in prenatal testing may have downstream effects on pregnant patients and their infants, we could not capture other outcomes in this study, such as changes in pregnancy monitoring or termination after ultrasounds nor the details of GDM management for the patient during pregnancy nor infant after birth. These and other outcomes warrant examination in future studies.

This study also has important strengths. We leveraged three different and complementary datasets to improve study generalizability with the representation of different populations living in different communities with varying medical conditions. These three datasets capture several practice patterns both within and between health systems and across different payer-mix groups. Where we observed consistency across datasets, findings are likely to be similar in other health systems and patient populations as well.

In summary, while ultrasound-based testing in the first two trimesters was done later in gestation during the early phase of the COVID-19 pandemic in 2020, recommended second trimester testing was largely completed as indicated. The changes in receipt of first trimester testing, specifically first trimester ultrasound, may have potential downstream effects on pregnant patients and warrants attention and further study. Although the COVID-19 pandemic created a massive stress on the health care system, prenatal health care delivery was generally maintained thanks to the dedication and resilience of providers and patients who continued to prioritize second trimester testing.

Data availability statement

The datasets obtained, generated, and analyzed for this study may be requested through a data use agreement with Highmark, Penn Medicine, or Yale New Haven Health. Requests to access these datasets should be directed to *handleys@chop.edu*.

Ethics statement

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

The individual author Contributions are listed below. All authors agree to be accountable for the content of the work. SCH: conceived and designed the study, planned the analysis, interpreted the data, and drafted the manuscript. RL: aided in data collection and curation, performed the analysis, and helped write and critically revised the manuscript. LSL: aided in data collection and curation, performed the analysis, and critically reviewed the manuscript. MP: oversaw data collection, curation, and analysis, and critically reviewed the manuscript. NY: aided in data analysis and visualization and critical reviewed the manuscript. MS: contributed to the design of the study, interpreted the data and critically revised the manuscript. KM: interpreted the data and critically revised the manuscript. JG: contributed to the design of the study, interpreted the data, and critically reviewed the manuscript. KD: interpreted the data and critically reviewed the manuscript. JFC: helped to conceive and design the study, plan the analysis, interpret the data, critically reviewed the manuscript, and helped oversee the study. HHB: conceived and designed the study, plan the analysis, interpret the data, critically reviewed the manuscript, and oversaw the study. All authors contributed to the article and approved the submitted version

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1064039/full#supplementary-material.

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Perinatal/maternal-fetal-infant dermatologic manifestations of SARS-CoV-2. An Overview and Implications for diagnosis, treatment, and prognosis

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Early identification of the dermatologic manifestations of SARS-CoV-2 in perinatal and maternal-fetal-infant populations is essential for early intervention in the diagnosis, treatment, and prevention of short and long term sequelae. Although cutaneous signs of SARS-CoV-2 are less common in pregnant women, neonates, and infants, the recognition of related skin lesions with regard to timing, location, duration, and pattern can lead to determining disease severity. While many pediatric patients may be asymptomatic with negative SARS-CoV-2 testing, skin lesions may be the only clue of infection. SARS-CoV-2 infection in pregnancy can lead to severe life threatening illness and by understanding the cutaneous manifestations associated with SARS-CoV-2 infection, early diagnosis can be made with improved maternal-fetal outcomes. A wide array of dermatologic presentations associated with SARS-CoV-2 are reported in the literature. This review explores the expanding reports in the literature of the dermatologic presentations of skin lesions related to SARS-CoV-2 specifically in perinatal and maternal-fetal-infant health and the implications for management. The collaboration of the specialties of dermatology, pediatrics, obstetrics/gynecology, and infectious disease in the approach to SARS-CoV-2 disease can lead to a better understanding of the scope and presentation of this disease.

KEYWORDS

SARS-CoV-2, pregnant women, neonates, infants, dermatologic patterns, skin

Introduction

Since the first report and isolation of SARS-CoV-2 infection in December 2019 in Wuhan, China, more than 600 million people have been infected globally causing over 6.4 million deaths (1). The ability to predict SARS-CoV-2 disease course and prevent transmission remains challenging but identifying dermatologic manifestations may have diagnostic and prognostic implications. Early reports of adverse effects associated with pregnancy were scarce but recent comparison studies present evidence that pregnant women with SARS-CoV2 have an increased susceptibility to hospitalization and severe illness (2, 3). The incidence of neonatal and infant

SARS-CoV-2 infection is less common than adults but when infected have the potential for serious complications (3–5).

Dermatologic manifestations of SARS-CoV-2 were first reported in March 2020 by Recalcati (6) with the description of infected patients presenting with an erythematous vesicular and urticarial eruption. Subsequently, multiple varying presentations in infected patients were eventually categorized into distinct patterns. Certain types of skin patterns are associated with more severe SARS-CoV-2 infections and can help establish the timeline of the disease process. Skin manifestations of SARS-CoV2 must be differentiated from diseases that normally be seen or exacerbated in pregnant women, neonates, and infants. A team approach of dermatologists, obstetricians, neonatologists, pediatricians and infectious disease specialists is ideal to optimize patient care.

Immunology

There is a complex interplay of physiologic immunological responses in healthy pregnant women, neonates, and infants that may affect SARS-CoV-2 susceptibility and skin disease presentation (7). Natural immunological shifts in pregnancy to protect the fetus result in down regulation of cell mediated immunity and upregulation of humoral immunity responses. The results are decreased T helper 1 cell (Th1) cytokine production (interleukin-12 (IL-12), interferon-gamma (IFN γ) and increased T helper 2 cell cytokines (IL-4, IL-10) (7, 8). Cytokines are needed for cell signaling and development of healthy neonates and infants especially with respect to adaptive immune responses. Innate decreased expression of IFN γ and tumor necrosis factor-alpha (TNF-α) in neonates and infants is postulated to be associated with increased susceptibility to infection (8–11). Physiologic cytokine alterations may lead to exacerbation of skin diseases in pregnancy (10).

Serious SARS-CoV-2 complications are attributed to a viral stimulated hyperinflammatory state leading to immunological responses and an exaggerated release of cytokines ("Cytokine Storm") (12). Among the main inflammatory mediators associated in this process are IFN γ, IL-6, and TNF-α, prime mediators involved in the physiological immune shifts in pregnant women, neonates and infants and in the pathogenesis of certain SARS-CoV-2 skin manifestations (13, 14). Tanacan et al. (13) reported in a study of 90 SARS-CoV-2 infected pregnant women that severity of illness correlated with elevation of IFN γ, IL-6 and D-Dimer and lower levels of IL-2, IL-10, and IL-17.

The combination of immunologic responses in pregnant women, neonates and infants with SARS-CoV-2 and skin disease results in a challenging complicated clinical picture created by the interactions of cytokines and pathophysiologic mechanisms (15).

Dermatologic patterns

Several main dermatological patterns associated with SARS-CoV-2 have been categorized and should be recognized in pregnant women, neonates and infants (16–20). Although patients with SARS-CoV-2 can present with polymorphic skin lesions, six common patterns have been described in the literature as (1) maculopapular (2) urticarial (3) vesicular (4) chilblain-like (5) livedo and (6) purpuric-vasculitic patterns (19, 20). The first 3 groups comprise lesions that are inflammatory and exanthematous and the latter 3 categories including cutaneous vasculitic disorders and vasculopathies (16, 17). These patterns have been noted in other skin diseases in pregnancy, neonatology and infancy recognizing the importance of a keen differential dermatologic diagnosis. **Table 1** summarizes SARS CoV-2 dermatologic patterns and relevant clinical aspects to pregnant women, neonates, and infants.

Maculopapular

Maculopapular exanthems appear to be the most prevalent of all patterns. In a case series of 375 patients with SARS-CoV-2 infection, 47% presented with maculopapular lesions (17). In smaller case studies, the prevalence varied from 5%–70% (19). The exanthem can occur at any age consisting of small red raised and flat lesions which typically appear on the trunk and spread to the extremities but may appear on the face and neck (**Figure 1**).

The eruption may or may not be associated with pruritus. The lesions are most notably observed during the mid course of infection when the patient is most symptomatic. A few studies have reported a latent onset up to 27 days after diagnosis (21, 22). Variants of this exanthem have been reported as purpuric-like, erythema-multiforme-like, pityriasis-rosea- like, erythema elevatum diutinum-like and perifollicular patterns (23).

The majority of patients with maculopapular lesions tend to have an uneventful course, but there are reports of SARS-CoV-2 infected pregnant women presenting with only maculopapular eruptions devoid of constitutional symptoms with premature rupture of membranes (24). Rare cases of transplacental transmission of SARS CoV-2 have been reported in maternal infections with maculopapular lesions (25–28). Oropez et al. (25) reported a case of a 34 year old pregnant woman with a diamniotic dichorionic twin pregnancy presenting with mild SARS Co-V-2 infection and a maculopapular eruption in the 3rd trimester. Healthy twins delivered by cesarean section revealed one twin was positive for SARS Co-V-2 IgG antibodies while the other twin was serologically negative. Placental pathology was negative for evidence of

TABLE 1 Summarizes SARS CoV-2 associated dermatologic patterns and relevant clinical aspects in pregnant women, neonates, and infants.

SARS CoV-2 associated dermatologic patterns: relevance in pregnant women, neonates and infants

Patterns	Features	Timing	Differential DX	Key points
Maculopapular	Most common Age variable Blanching erythematous macules/ papules; +/− pruritus Trunk- diffuse spread	Mid-course/symptomatic (Early/Late onset reported)	Drug, Viral (Parvo B-19, Measles, Rubella, HHV6, Enterovirus, Adenovirus) Streptococcal, Syphilis Pregnancy: PEP, AEP Neonate: ETN Neonate/Infant: Miliaria, Atopic Dermatitis	Favorable prognosis Cases reports: Preterm labor, Premature rupture of membranes, Transplacental viral transmission;? Trigger - antiviral therapy
Urticarial	Age/Prevalence variable Female tendency Transient wheals;++pruritus Trunk to acral/face spread	Prodromal/asymptomatic (Symptomatic pts reported with mod/severe disease)	Drug, Viral (CMV, RSV, EBV, HSV), Mycoplasma, Parasitic, Food, Allergy, Idiopathic Pregnancy: PEP Neonate/Infant: Infections, Food, Drug, Atopy	Can be associated with severe SARS CoV-2 Difficult to differentiate from other infections/ drug rx PEP- 3rd trimester, begins abdominal striae, longer duration than SARS COV2 urticaria
Vesicular	Less common Adults-reported in children Vesicles +/− purpura; +/− pruritus Trunk - localized or diffuse	Mid-course/symptomatic (Early/Late onset reported)	VZV, HSV, Enterovirus, Echovirus, Impetigo Scabies, Miliaria, Dermatitis, Drug, Autoimmune Pregnancy: Pemphigoid Gestationis Neonate/Infant: ETN, Acropustulosis of Infancy HyperIgE, Histiocytosis	Specific skin SARS CoV-2 manifestation May be helpful in early diagnosis Can be associated with mod-severe disease Eliminate other viral/bacterial: serious fetal sequelae
Chilblain-like	Prevalence variable Young adults/children Erythematous/violaceous macules papules/nodules Toes/Fingers	Late onset/asymptomatic/ mild disease	Idiopathic or Secondary (Autoimmune-CLE, Antiphospholipid disease), Cryoglobulenemia, Raynaud's disease, Hematologic, Neoplastic	Most familiar skin SARS CoV-2 manifestation Mild disease course -resolves 1-2 weeks Late onset -may be only sign of SARS CoV-2 Evaluate for Hypercoagulable or Autoimmune disease
Livedo	Less common Prevalence- elderly Mottled erythema/violaceous Net-like discoloration/purpura Distal extremities to diffuse spread	Mid-course/symptomatic	Idiopathic, Physiologic, Autoimmune, Hematologic Viral, Bacterial, Drug, Neurologic Pregnancy: SLE, Antiphospholipid Disease, Erythema Ab Igne Neonate/Infant: CMTC, Erythema Ab Igne, HSP	Livedo Reticularis - mild disease course Livedo Racemosa - severe disease course/ coagulopathy Livedo Pattern and pregnancy - risk of severe disease Neonate/Infants - Livedo pattern unusual in SARS COV2
Purpuric/ vasculitic	Least common Age variable Hemorrhagic macules/papules Palpable purpura Distal extremities to diffuse spread	Mid–course/symptomatic Diffuse = severe infection	Viral (Hepatitis, HIV) Bacterial (Meningococcus) Drug, Hematologic, Autoimmune, Neoplastic Nutritional disorders (Vitamin C deficiency) Pregnancy: SLE, TTP, ANCA-Associated Vasculitis Neonate/Infant: HSP, Kawasaki's Disease, MIS	Severe morbidity/mortality Skin-Prognostic sign Kawaski's like/MIS-C/MIS-N associated = severe disease

AEP, atopic eruption of pregnancy; ANCA, anti-neutrophil cytoplasmic antibody; CLE, cutaneous lupus erythematosus; CMTC, cutis marmorata telangiectatica congenita; CMV, cytomegalovirus; EBV, epstein barr virus; ETN, erythema toxicum neonatorum; HHV6, human herpesvirus 6; HIV, human immunodeficiency virus; HSP, henoch schonlein purpura; HSV, herpes simplex virus; MIS, multisystem inflammatory syndrome; Parvo B19, parvovirus B-19; PEP, polymorphic eruption of pregnancy; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; VZV, varicella zoster virus.

SARS-Co-V-2. Maculopapular exanthems have been reported in infants with SARS-CoV-2 infection in association with mild symptomatic disease (17). The primary differential diagnosis includes other viral infections or adverse drug eruptions (**Table 1**). SARS-CoV-2 antiviral therapy can produce drug reactions appearing identical to viral eruptions making identification of the inciting agent challenging (14).

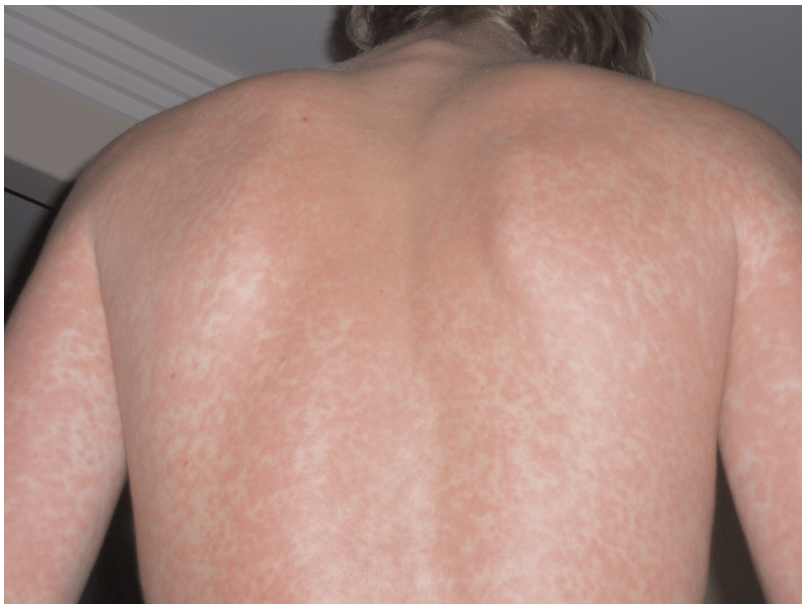

FIGURE 1
Maculopapular pattern.

Polymorphic Eruption of Pregnancy (PEP) (Synonym-PUPP Pruritic Urticarial Papules and Plaques of Pregnancy) and Atopic Eruption of Pregnancy (AEP) may present in pregnant women as maculopapular lesions (29). Erythema toxicum neonatorum (ETN), miliaria, and atopic dermatitis could appear with maculopapular lesions in neonates and infants (30, 31). It is imperative to consider SARS CoV-2 infections in the differential of maculopapular eruptions in pregnant women, neonates and infants for proper intervention to prevent complications and transmission.

Urticarial

Urticarial lesions seen in SARS CoV-2 are generally encountered during the prodromal asymptomatic period of disease and may be the first sign of disease (**Table 1**). The incidence of urticaria in SARS-CoV-2 infection ranges from 16.7%–19% and has a higher prevalence in females (17, 32, 33). Although several studies have reported SARS CoV-2 associated urticaria primarily in adults, several cases have been documented in children (34). The lesions generally last a week and have been associated with moderate to severe complications in some patients (17). Hive-like, blanching thin plaques which are transient and changeable in shape with severe pruritus typically present on the trunk and spread to the extremities possibly affecting the face and acral areas (**Figure 2**). Angioedema and urticarial vasculitis may also occur (33).

Urticaria secondary to SARS CoV-2 may be difficult to differentiate from other causes such as medications, food, bacterial, parasitic, other viral infections, allergic reactions and idiopathic urticaria (33, 34). Pathophysiologically, SARS-CoV-2 stimulates mast cell degranulation through either direct viral contact or complement activation and cytokine release. It is theorized serious end organ damage in SARS-CoV-2 infection is due to mast cell activation (13, 35, 36).

With respect to pregnancy, the primary skin disease to differentiate other than drug or infection is PEP (29, 37). PEP tends to occur late in the 3rd trimester or in the post-partum period usually in primigradas and begins within the abdominal striae. Unlike PEP, SARS-CoV-2 associated urticaria tends to resolve around 7 days (17). Newer reports have shown that chronic urticaria can develop particularly in young women after SARS-CoV-2 infection or SARS-CoV-2 vaccines (38, 39). The most common etiologic factors in the differential of urticaria in neonates and infants include infection, food, medications and atopy (40).

SARS-CoV-2 should be considered in the differential diagnosis of urticaria in pregnant women, neonates, and infants without constitutional symptoms due to the possibility of moderate to severe disease complications.

Vesicular

Vesicular eruptions in SARS-CoV-2 were first described as "varicella-like" in April 2020 by Marzano (20). Usually

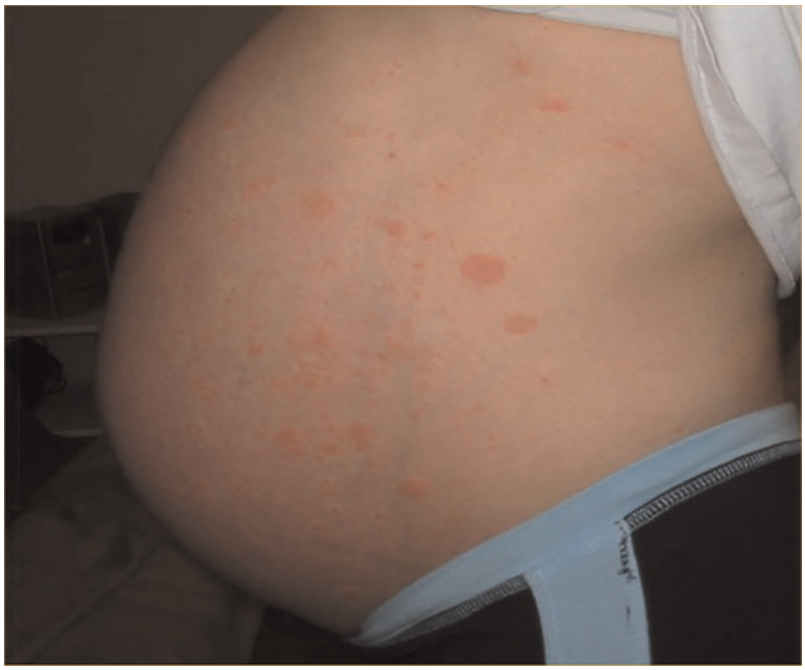

FIGURE 2
Urticarial pattern.

appearing on the trunk, scattered fluid filled blisters may appear localized or diffusely with or without purpura (**Figure 3**).

The prevalence ranges from 3.7%–15% occurring primarily in adults but has been reported in children (17, 19, 32, 41). SARS-CoV-2 vesicular exanthems are associated with moderate severity of illness and occur when patients are symptomatic in mid course of disease. Cases of early or late onset of vesicular lesions have been reported. The median duration of the eruption is approximately 8–10 days (17, 19, 20, 32). Vesicular eruptions associated with SARS CoV-2 are considered to be specific to the virus and may be useful diagnostically. In a systematic review, Jamshidi reports that vesicular lesions may be associated with neurologic symptoms including headache, dysgeusia, and confusion (42). The pathogenesis of vesicular lesions in SARS-CoV-2 is felt to be related to either a direct cytotoxic effect on dermal vessel endothelium or exaggerated release of cytokines (19, 41).

SARS-CoV-2 infection must be considered in the differential diagnosis of vesicular eruptions in pregnant women, neonates and infants. Causes to be eliminated include viral and bacterial infections, infestations, miliaria, irritant or contact dermatitis, and autoimmune diseases (19, 43, 44) (**Table 1**). Viruses such as herpes simplex virus (HSV), varicella zoster virus (VZV), measles, and rubella are associated with serious fetal sequelae and must be differentiated (45). HSV and VZV reactivation has been associated with SARS-CoV-2 infection with some patients developing more severe illness (46–48). Flaring of atopic dermatitis can present as vesicular lesions in pregnancy and infancy with secondary staphylococcal or HSV infection requiring immediate therapeutic intervention. Elevated IL-4 levels in pregnancy may be a factor in the exacerbation of atopic dermatitis (49). Common transient conditions in neonates may present with vesicular lesions (ETN, acropustulosis of infancy) or rare conditions such as Hyper IgE syndrome, or histiocytosis (50, 51). Pemphigoid Gestationis, a rare immunobullous disease in pregnancy, usually occurring in the 3rd trimester with periumbilical bullae should be included in the differential diagnosis of SARS-CoV-2 vesicular exanthems (29).

Chilblain-like

Chilblain-like or "pernio-like" vascular skin lesions of the hands and feet are probably the most recognized of all skin lesions associated with SARS-CoV-2. Multiple reports of non-blanching erythematous or violaceous lesions of the toes associated with SARS-CoV-2 infection help to coin the term "Covid toes" (19, 52) (**Figure 4**).

Usually seen in asymptomatic or mildly infected young adults and children, SARS-CoV-2 chilblain-like lesions tend to appear late in the course of infection. Numerous studies report the prevalence varies from 14.3%–72% (19). Chilblain and pernio diseases are vascular inflammatory reactive skin

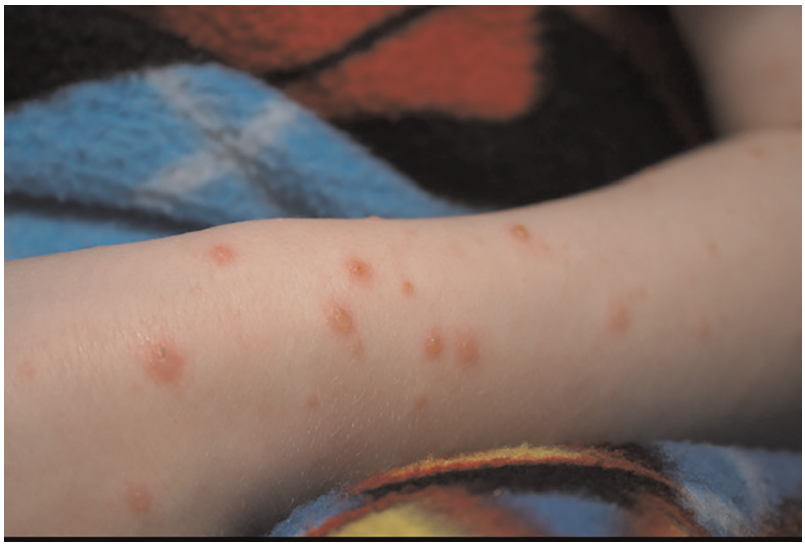

FIGURE 3
Vesicular pattern.

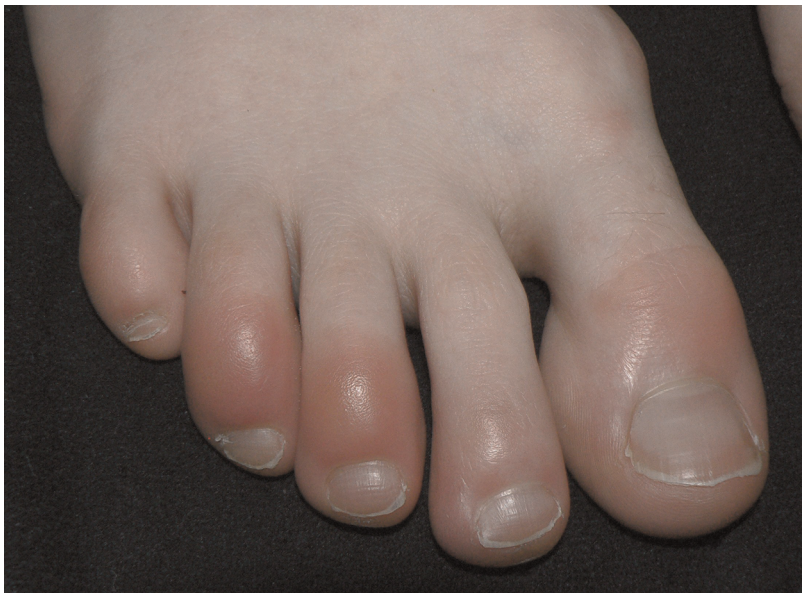

FIGURE 4
Chilblains pattern.

disorders to environmental stimuli such as cold exposure or damp humid environments. The hands and feet are primarily affected with a vasoconstrictive response and resultant erythematous, violaceous macules, papules or nodules of the fingers or toes. The most common symptoms are pain and pruritus. SARS-COV-2 associated chilblain-like lesions tend to last 1–2 weeks after the onset of symptoms and resolve without incident (32). Primary chilblain/pernio disease is idiopathic but secondary causes include autoimmune [systemic lupus erythematosus (SLE), antiphospholipid disease, Raynaud's disease] cryoglobulinemia, and hematologic diseases (52). There is controversy whether there is a direct association between SARS-CoV-2 infection and chilblain-like lesions. Colmenero (53) demonstrated the presence of SARS-

CoV-2 in endothelial cells of pernio-like lesions by electron microscopy. On the contrary, many patients presenting with chilblain-like skin lesions tested negative with reverse transcription polymerase chain reaction test (RT-PCR), had negative serology, or were not tested at all (54, 55). This may be explained by robust protective levels of IFN-1 in younger patients or the significant variability of current testing. It has been proposed that chilblain-like lesions represent late manifestations of SARS-CoV-2 due to a delayed immunological reaction or an inappropriate type 1 interferon response (56). A literature review by Cappel et al. (56) suggested that the pathogenesis of SARS-CoV-2 chilblain-like lesions involves complex interactions between the virus, angiotension converting enzyme-2 (ACE-2), the renin-angiotension-aldosterone system, sex hormones, and interferon type 1 responses causing endothelial cell dysfunction (56–58).

Histopathology of skin lesions is similar to that found in idiopathic chilblains with epidermal necrotic keratinocytes, dermal edema, perivascular and perieccrine lymphocytic inflammation and microthrombi in the vasculature and endothelial cell inflammation (58).

Chilblain-like lesions may be the only sign of SARS CoV-2 in pregnant women, neonates and infants late in the disease course so it is important to properly diagnose this pattern and differentiate from other primary or secondary causes.

Livedo

Livedo patterns are less common manifestations of SARS CoV-2 ranging from 4%–6% (17, 19, 41). Infected patients presenting with livedo reticularis-like lesions tend to have milder disease and transiently clear over a period of 2 weeks with the average duration approximately 9–10 days (17, 19, 59, 60). The lesions appear as a mottled red-blue-purple net-like discoloration on the trunk, flexor forearm surface, dorsal hands and feet (**Figure 5**).

A pauci-inflammatory thrombogenic vasculopathy is noted on histopathology with serologic elevated D-Dimer levels (14, 61). It is theorized that the SARS CoV-2 virus directly infects endothelial or smooth muscle vessel cells causing low grade vascular inflammation and vasodilation. This process results in decreased blood flow with deoxygenated hemoglobin but no thromboembolism (60). Livedo reticularis must be differentiated from other causes including either physiologic, secondary, or idiopathic (**Table 1**).

Livedo racemosa is a more severe variant and is characterized by larger more widespread mottling of the skin that is generally secondary to a pathologic condition. Usually appearing in elderly patients with severe SARS-CoV-2 infection, the lesions can be transient or persistent and appear mid course during active symptoms. In contrast to livedo reticularis, patients presenting with livedo racemosa may develop severe coagulopathy and complications. Galvan Casas et al. (17) reported a mortality rate of 10% in patients presenting with livedo racemosa. Pathologically, vessels are partially occluded which leads to retiform purpura and complete vascular occlusion. Histologically, there is a micro thrombotic vasculopathy with possible dermal arterial thrombosis (62).The vasculopathy is thought to be due to direct viral effects or immune stimulation of the complement cascade with the release of proinflammatory cytokines (IL-6, IL-8, IFN γ, TNF-α) elevated D-Dimer levels, and fibrinogen degradation products which are associated with thrombosis and increased mortality (61, 62). Severity of SARS- CoV-2 illness in pregnant women may be correlated with elevated IFN γ, IL-6, and D Dimer levels (13).

In pregnant women, neonates and infants, livedo patterns can be seen associated with other hypercoagulable diseases including SLE and antiphospholipid antibody syndrome. Interestingly, antiphospholipid antibodies are found in SARS-CoV-2 patients with severe illness, livedo lesions, and severe thrombosis. In a study by Sangle et al. (63), widespread livedo reticularis is thought to be an independent factor of pregnancy complications in patients who have negative antiphospholipid antibodies with or without lupus. Rodriguez et al. (64) reported a case of an infant presenting with livedo racemosa and respiratory failure diagnosed as multisystem inflammatory syndrome (MIS-C). Given the high risk for severe complications of SARS-CoV-2, infected pregnant women, neonates and infants presenting with livedo patterns should closely be monitored and investigated for impending thrombotic events.

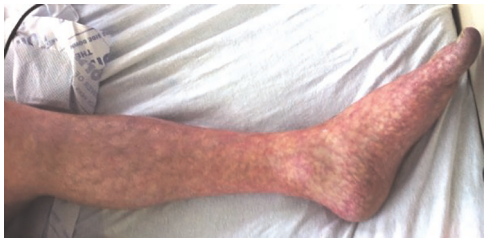

FIGURE 5
Livedo pattern.

Purpuric/vasculitic

Vasculitic or purpuric lesions in SARS CoV-2 infected patients are associated with severe morbidity and mortality (17, 52). Less common than other patterns, various studies report a prevalence of 3%–8% and the lesions occurring during the symptomatic phase of infection(17, 19, 20, 32).

The lesions appear as non-blanching hemorrhagic macules, patches, bullae, or palpable purpura on the extremities or acral areas (**Figure 6**).

Distal acral ischemia may occur leading to necrosis and gangrene of the digits (44). Diffuse spread of vasculitic lesions correlates with severe sequelae (65–67). Elevated D-Dimer and fibrinogen degradation products were found in patients with distal ischemia with some developing disseminated intravascular coagulation (68). Histologically, a true vasculitis is seen with a neutrophilic infiltrate within the small vessel walls, intense lymphocytic perivascular infiltrate, fibrin deposition, and endothelial swelling differentiating this pattern from livedo lesions (43).

Purpuric, petechial, or vasculitic lesions may be present in other viral infections in pregnant women, neonates and infants including hepatitis, human immunodeficiency virus, parvovirus B19 as well as bacterial infections, hematologic, autoimmune and nutritional disorders (45) (**Table 1**). Adverse drug reactions including antiviral agents are common causes of purpuric vasculitic eruptions in SARS Co-V-2 due to the multitude of therapeutics in severe illness (19). Systemic lupus erythematosus, thrombotic thrombocytopenic purpura, anti-neutrophil cytoplasmic antibody associated vasculitis, and parvo B-19 infections are included in the differential diagnosis of purpuric vasculitic lesions in pregnancy and can lead to serious perinatal and fetal complications (45, 69–71). Although rarely seen in this age group, Ig A vasculitis (Henoch Schonlein Purpura -HSP), Kawasaki's disease, and multisystem inflammatory syndrome should be considered in the differential diagnosis in neonates and infants with purpuric or vasculitic lesions and diagnosed promptly to prevent potential complications (72–74).

Pathogenesis of SARS-CoV2 petechiae/purpura/vasculitis is thought to be due to direct viral damage to endothelial cells causing endotheliitis and endothelial cell injury or a dysregulated inflammatory responses with immune complex deposition and massive cytokine release. Macrophage activation results and leads to the thrombotic lesions and events seen in SARS CoV02 coagulopathy (75).

Recognizing specific skin lesions may be prognostic in disease severity. Vasculitis, livedo racemosa, and distal ischemia are associated with more severe complications while

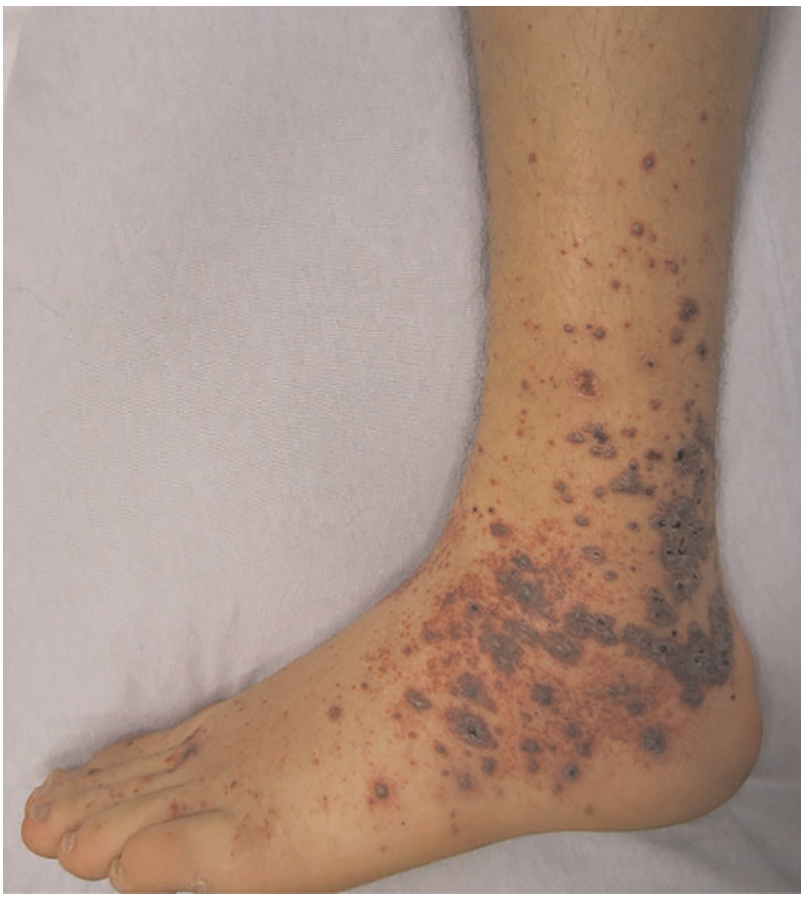

FIGURE 6
Purpuric/vasculitic pattern.

chilblains-like lesions have the highest survival rates. The importance of identifying skin manifestations in SARS-CoV-2 infected pregnant women, neonates, and infants is imperative to allow early intervention and therapeutic management.

Multisystem inflammatory syndrome

Early reports of SARS-CoV-2 infection indicated that children and neonates tended to be spared of severe associated complications. In 2020, a hyperinflammatory syndrome with characteristics similar to Kawasaki's Disease (KD) was reported in children with concurrent or post SARS-CoV-2 infection (73, 74). The syndrome was labeled as Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2 (PIMS-TS) and in neonates as Multisystem Inflammatory Syndrome in Neonates (MIS-N) (76–78). Although the incidence is rare, MIS-C is a potentially life threatening variant leading to severe complications including cardiac injury, multiorgan failure and death, The most commonly involved organ systems are gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory. Overall, pediatric mortality due to MIS-C is reported at 1.9% but in neonates and young infants it may be as high as 9% (79).

MIS-C usually occurs in children aged 9 years (ranging 1 month to 20 years) and in neonates (MIS-N) from within 7 days to 27 days post birth (77–79). The CDC criteria for MIS-C/MIS-N includes persistent fever(not MIS-N), 2 organ system involvement, laboratory evidence of inflammatory markers, laboratory evidence of current or recent SARS-CoV-2 infection or maternal infection, and no other plausible disease causing the syndrome (79, 80).

Cutaneous and mucocutaneous lesions are present in approximately 73% of children with MIS-C (81). Maculopapular exanthems and conjunctivitis are the most commonly reported skin signs. Facial erythema or periorbital edema ("Heliotrope rash"), hand and foot edema, perineal erythema, desquamation, and cracked lips are noted features. Retiform purpura, targetoid lesions, urticaria and erythroderma have been described (81). Godfred-Cato et al. (82) reported skin rash was the most common presenting sign of MIS-C in infants less than 12 months of age and 32.9% of these infants required ICU admission. The appearance of a maculopapular rash in MIS-C may have prognostic implications depending upon the presentation. In a small study by Rekhtman (83), some MIS-C patients specifically presenting with maculopapular lesions had lower levels of inflammatory markers, less ICU admission, less mechanical ventilator support, and less serious consequences. In contrast, isolated purpuric and necrotic lesions have been noted in neonates with MIS-N with cardiogenic shock, elevated inflammatory markers, and multiorgan failure (84).

MIS-C patients with a Kawasaki's disease-like (KD-like) presentation have been reported. Similar lesions include conjunctival injection, hyperemic cracked lips, strawberry tongue, and coronary artery disease with severe complications. While classic KD patients tend to be younger (less than 5 years), MIS-C with KD-like disease patients are usually older (5–13 years) and present with more gastrointestinal symptoms. Both MIS-C/KD-like disease and KD patients may present with severe cardiac involvement but KD patients tend to have severe persistent sequelae. There are reports of persistent cardiac dysfunction in some MIS-C patients (85, 86).

The pathogenesis of MIS-C and MIS-N is unknown but theorized to result from autoantibody mediated complexes to SARS-CoV-2 infection through the respiratory or gut mucosa (87). Neonates may develop immune complexes derived from exposure to maternal antibodies (79). Others postulate that SARS-CoV-2 virus acts as a superantigen causing an exaggerated release of inflammatory mediators leading to cytokine storm (88). Consiglio (87) reported that MIS-C patients had lower levels of TNF-α and normal IL-6 levels both of which are elevated in acute SARS-CoV-2 infection casting doubt on the cytokine storm theory. The efficacy of intravenous immunoglobulin therapy in MIS-C supports an autoantibody mediated pathogenesis (87).

Although there are no diagnostic skin manifestations, cutaneous and mucosal lesions may be the presenting signs of MIS-C or MIS-N, early recognition of dermatological manifestations can lead to timely diagnosis and intervention (85).

Less common skin manifestations of SARS-CoV-2

Unusual skin manifestations associated with SARS-CoV-2 have been reported with regard to maternal/fetal/infant health. Vertical transplacental transmission of SARS CoV-2 is rare but has been reported with possible associated skin manifestations. Generalized and local fetal skin edema diagnosed by ultrasound has been reported in pregnant women with SARS-CoV-2 infection (89). Associated elevated serological maternal levels of IL-6 and D-Dimer levels leading to cytokine stimulated inflammation or direct viral cytotoxicity is felt to alter the neonatal cutaneous microbiome resulting in fetal skin edema (89, 90). Necrotic lesions of the upper arm leading to amputation were noted in a neonate born to a SARS-CoV-2 infected mother and theorized that the virus may induce neonatal thrombotic events through exposure to maternal infection (91). Unusual orange discoloration of the skin was reported in a SARS-CoV-2 infected family in which yellow to brown macules were noted on the extremities of a newborn and yellow-brown discoloration of the palms and soles found on the other family members. The virus is thought to cause abnormalities

in the conversion or transport of beta-carotene causing excess amounts to be deposited in the skin (92). Acute Hemorrhagic Edema of Infancy has been described in a SARS-CoV-2 infected infant which recurred 3 weeks after initial presentation and resolution (93). More evidence is needed to determine the relationship of neonatal infant skin eruptions and maternal SARS CoV-2 infections.

Conclusion

There are limited reports on the relationship of SARS-Co-V-2 infection and related dermatologic manifestations in pregnant women, neonates and infants but reports have demonstrated this patient population is at high risk for SARS-Co-V-2 complications. Skin lesions may be the first sign of infection and be prognostic for disease severity. Severe morbidity and mortality have been associated with the appearance of purpuric and vasculitic lesions and less commonly with chilblains-like lesions. By identifying skin manifestations in SARS-Co-V-2 infected pregnant women, neonates, and infants, asymptomatic infections may be properly diagnosed, disease transmission prevented, and severe disease complications averted. It is important to differentiate other skin diseases which can flare during pregnancy or in the neonatal/infancy period due to physiologic immunological shifts. The collaboration between dermatology, obstetrics and gynecology, neonatology, pediatrics, and infectious disease can optimize perinatal/maternal-fetal-infant health care in the diagnosis and treatment of SARS- CoV-2.

Author contributions

EY drafted the manuscript. The author was the sole contributor to the article and approved the submitted version.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1071839/full#supplementary-material.

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Provision of mother's own milk for preterm infants during the COVID-19 pandemic: Differential effect of insurance

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Mother-infant dyads faced many challenges during the COVID-19 pandemic; however, the impact was different depending on socio-economic determinants. This study aims to investigate the impact of the COVID-19 pandemic on maternal provision of mother's own milk (MOM) at neonatal intensive care unit (NICU) discharge among preterm infants. We hypothesized that fewer infants would be discharged home on any MOM during the pandemic period compared to a pre-pandemic period. This is a retrospective analysis of infants born <34 weeks' gestation admitted to the Women and Infant's Hospital NICU. Infants born pre-pandemic (1/1/2019 to 2/29/2020) were compared to infants born during the pandemic (3/1/2020 to 4/30/2021). Maternal and neonatal variables were analyzed by group. The primary outcome was provision of MOM (defined as feeding exclusively MOM, or a combination of MOM and formula) at NICU discharge. Analyses were performed for time periods, and multivariable regression analyses were run for the total cohort and by insurance type. Analysis included 268 infants born pre-pandemic and 262 infants born during the pandemic. Pandemic group mothers vs. pre-pandemic were less likely to be single (27%, 63/233 vs. 38%, 93/243; $p = 0.01$) and more likely to have a diagnosis of chorioamnionitis (16%, 38/236 vs. 7%, 17/243; $p = 0.002$). Rates of public insurance were similar (55% pre-pandemic and 50% pandemic). There was no significant change in provision of MOM between time periods. In multivariable analysis, public insurance decreased the odds of MOM at discharge for the entire study period (aOR 0.31, 95% CI: 0.19–0.50; $p = 0.0001$). On analysis by insurance type, rates of MOM increased from 77% pre-pandemic to 88% during the pandemic ($p = 0.03$) for mothers with private insurance and remained unchanged for mothers with public insurance (52% pre-pandemic and 53% pandemic; $p = 0.86$). Mothers with private insurance had twice the odds (aOR 2.02, 95% CI: 1.02–3.97; $p = 0.04$) of providing MOM during the pandemic vs. pre-pandemic. For those with public insurance, the odds for any MOM provision during the pandemic were unchanged (aOR 0.95, 95% CI: 0.5–1.7; $p = 0.86$). These differences may be related to health care disparities requiring additional exploration of risk factors and the need for equitable opportunities for all mother-infant dyads.

KEYWORDS

mother's own milk, neonatal intensive care unit (NICU), preterm (birth), coronavirus disease 2019 (COVID-19), pandemic, insurance, breast milk

Introduction

Mother's own milk (MOM) is the ideal source of nutrition for infants, and in particular for infants born prematurely. MOM is beneficial in decreasing the risks of necrotizing enterocolitis, chronic lung disease, and late onset sepsis, and is associated with improved neurodevelopmental outcomes (1, 2). Yet despite these benefits, fewer preterm infants than term infant receive breast milk. In a recent report published by the Centers for Disease Control and Prevention, among infants born in the United States, 71.3% of preterm infants receive breast milk comparted to 84.6% of term infants (3). Unfortunately, there are known multi-factorial socioeconomic challenges such as poverty, low maternal education, and maternal race and ethnicity that are linked to decreased provision of MOM (4–8). Authors of a recent California cohort study reported a 52% lower odds of breast milk use at Neonatal Intensive Care Unit (NICU) discharge for families with public insurance compared to those with private insurance (8).

The onset of COVID-19 brought about unexpected and swift changes in the NICU environment. Early in the pandemic, NICU visitation policies were restrictive, limiting the number of parents who could visit as well as the frequency of visits. Such changes led to parental reported difficulties with breastfeeding, bringing in milk and supplies, communication and teaching moments, as well as overall decreased wellbeing (9–13). Additionally, many units experienced staffing changes that included scaled-down in-person lactation support (9, 14-16).

Currently, there are limited data published on the early impact of the pandemic on the provision of MOM for high-risk preterm infants, particularly between mothers with different insurance types. The primary aim of this study was to investigate maternal provision of MOM at the time of NICU discharge among preterm infants, and second, MOM provision for mothers with public vs. private insurance. Our primary hypothesis was that fewer infants would be discharged home on any MOM during the pandemic when compared to pre-pandemic.

Methods

This is a single center, retrospective, observational study of preterm infants born <34 weeks gestational age (GA) at Women and Infant's Hospital (WIH) between January 2019 and April 2021 and who survived to NICU discharge. Exclusion criteria included infants with a congenital syndrome and infants who were transferred prior to discharge. The study protocol was approved by the WIH Institutional Review Board and informed consent was waived due to the retrospective nature of the study.

There were two comparison groups: infants born pre-pandemic (January 2019–February 2020), and infants born during the pandemic (March 2020-April 2021). March 2020 was selected as the start date of data collection for the pandemic group as per the World Health Organization (WHO) definition (17).

Maternal and infant data were collected from the electronic medical record and included the following variables: maternal age, marital status, insurance type (public vs. private), parity, multiple gestation, mode of delivery, presence of prenatal care, race, ethnicity, education level, and medical complications during pregnancy including maternal hypertensive disorders (inclusive of gestational hypertension, preeclampsia and eclampsia), gestational diabetes, placental abruption, and clinical chorioamnionitis. Infant variables included GA at birth, birth weight, sex, inborn status, discharge weight, length of hospital stay, and medical complications including sepsis (defined by a positive blood culture), bronchopulmonary dysplasia (defined as oxygen at 36 weeks), necrotizing enterocolitis (defined as Bell stage ≥2), and presence of a gastrostomy tube.

The primary outcome of this study was MOM at NICU discharge, which was defined as either feeding exclusively MOM or a combination of MOM and formula. All breast milk that infants received was MOM, as a donor human milk program was not in place at WIH during the study period.

Lactation support services

The WIH lactation support program is an in-person service that is available seven days per week, eight hours per day, and this availability was unchanged during the pandemic time period. The lactation support team is comprised of three Certified Lactation Counselors (CLCs), including a native Spanish speaker, and two nurse International Board Certified Lactation Consultants (IBCLCs). The team assists all NICU mothers in three main areas: milk expression, preparing to breastfeed, and breastfeeding. Additionally, the lactation support team provides post-NICU support, including phone consultations and as needed outpatient lactation appointments. The IBCLCs create unit breastfeeding/lactation guidelines, lead the NICU Breastfeeding Committee, and provide education for the NICU staff.

NICU visitation policy

The WIH NICU visitation policy was modified during the pandemic. The initial change restricted visitation to parents and grandparents only, with universal masking required. Within a week, visitation was further limited to two designated visitors per patient or set of multiples (typically

the mother, and their partner/support person). The two designated visitors could be modified under extenuating circumstances, and exceptions were made, pending approval by hospital administration, for critically ill or dying infants. Each visitor was allowed only one visit per day of unlimited duration.

If a designated visitor had any symptoms of COVID-19, they were asked not to visit the hospital and to receive polymerase chain reaction (PCR) testing. If a designated visitor was exposed to someone positive for COVID-19, they were asked to quarantine for 10 days and a negative PCR test after quarantine was required to visit the hospital. If a designated visitor was positive for COVID-19, they were asked to quarantine for 10 days. If a baby was born to a mother positive for COVID-19, they could not visit the baby in the NICU for 10 days after symptom onset, or positive PCR test if asymptomatic. All cases of COVID-19 symptoms, exposure and positive testing were reviewed by the hospital pediatric infectious disease specialist who advised on testing and quarantine requirements.

TABLE 1 Maternal characteristics and medical complications.

	Pre-Pandemic *n* (%)	Pandemic *n* (%)	*p* value
Maternal Characteristics	$n = 243$ (51%)	$n = 236$ (49%)	
Maternal age, years (mean ± SD)	30 ± 6	30 ± 6	0.59
Single	93/243 (38)	63/233 (27)	0.01
Public Insurance	134/243 (55)	119/236 (50)	0.30
Primiparous	119/243 (49)	131/236 (56)	0.15
Multiple Birth	39/243 (16)	33/233 (14)	0.57
Cesarean Delivery	152/241 (63)	133/232 (57)	0.20
No Prenatal Care	4/240 (2)	3/233 (1)	0.73
Maternal Hypertensive Disorder	76/241 (32)	71/235 (30)	0.75
Gestational Diabetes	25/242 (10)	31/236 (13)	0.34
Placental Abruption	27/241 (11)	32/236 (14)	0.43
Chorioamnionitis	17/243 (7)	38/236 (16)	0.002
Non-White	94/242 (39)	89/236 (38)	0.80
Hispanic	59/241 (25)	46/234 (20)	0.21
Less than high school graduate	23/243 (9)	21/236 (9)	0.71

Statistical analysis

Maternal and infant characteristics were compared in bivariate analysis by using the t test or Wilcoxon test for continuous variables, and χ^2 test for categorical variables. A multivariable logistic regression model was created to identify factors associated with the primary outcome of MOM at discharge. The model was adjusted for multiples, and pre-identified variables known to be confounders in the relationships of provision of MOM including maternal age, marital status, parity, race, education, and insurance status. Length of hospital stay was included to reflect infant health status. Models were run with clinical chorioamnionitis as it was significantly different between the time periods, however, was not retained as it did not contribute to the main regression model. Adjustment for multiple births was done using generalized estimating equations with an exchangeable correlation structure. Adjusted odds ratios were calculated with 95% confidence intervals. Secondary analyses were also conducted to study the relationship of insurance type and MOM at discharge. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute).

Results

A total of 479 mothers and 530 infants met inclusion criteria and were compared by pre-pandemic ($n = 243$ mothers and $n = 268$ infants) and pandemic ($n = 236$ mothers and $n = 262$ infants) time periods. Table 1 presents maternal characteristics. In the pandemic group, there were significantly fewer mothers who identified as single (27% vs. 38%, $p = 0.01$), and more cases of clinical chorioamnionitis (16% vs. 7%, $p = 0.002$) than pre-pandemic. Maternal social determinants of health including race, ethnicity, and education less than high school were similar between the two time periods. No differences were seen for public insurance pre-pandemic vs. pandemic (55% vs. 50%, $p = 0.30$). Table 2 presents infant characteristics. Infants born during the pandemic had a higher birth weight (1,481 g ± 528 g vs. 1,617 g ± 507 g, $p = 0.005$). This difference decreased but remained significant when controlling for GA ($p = 0.02$). Infant characteristics of medical complications, discharge weight, and length of NICU stay were similar between groups. For the primary outcome of any MOM at NICU discharge, analyzed by pre-pandemic vs. pandemic time periods, no significant differences (63% vs. 71%, $p = 0.07$) were seen for the total cohort. However, provision of any MOM at NICU discharge increased for mothers with private insurance during the pandemic (77% pre-pandemic vs. 88% pandemic, $p = 0.03$), while there was no change between time periods for mothers with public insurance (52% pre-pandemic vs. 53% pandemic, $p = 0.86$).

Table 3 presents the multivariable regression models to predict any MOM at NICU discharge. For the total cohort, there was no effect of the pandemic on maternal provision of any MOM at NICU discharge (aOR 1.3, 95% CI: 0.84–1.95; $p = 0.26$). However, public insurance was an independent risk factor for lower odds of MOM provision (aOR 0.31, 95% CI: 0.19–0.50; $p = 0.0001$), and lower maternal education was

associated with a 50% lower odds of MOM provision (aOR 0.5, 95% CI: 0.2–0.9; $p = 0.03$). In addition, for every 10 days in the NICU, there was a 13% decreased odds of MOM provision (aOR 0.87, 95% CI: 0.83–0.91; $p = 0.0001$).

Separate regression models (Table 3) were estimated to predict any MOM at discharge by insurance type. During the pandemic, the odds of any MOM at discharge for mothers with public insurance remained unchanged (aOR 0.95, 95% CI: 0.5–1.7; $p = 0.86$), with a 18% decrease in odds of any MOM (aOR 0.82, 95% CI: 0.8–0.9; $p = 0.0001$) for every 10 additional days in the NICU. Mothers with private insurance had twice the odds of providing any MOM at NICU discharge (aOR 2.02, 95% CI: 1.02–3.97; $p = 0.04$), with a 9% decrease in odds of any MOM (aOR 0.91, 95% CI: 0.84–0.98; $p = 0.02$) for every 10 additional days in the NICU. Being single was associated with lower odds (aOR 0.4, 95% CI: 0.2–0.99; $p = 0.048$) of providing MOM at discharge for the private insurance group. Lower maternal education was marginally associated with lower odds (aOR 0.4, 95% CI: 0.2–0.99; $p = 0.047$) of providing MOM for the public insurance group only.

TABLE 2 Infant characteristics and medical complications.

	Pre-Pandemic *n* (%)	Pandemic *n* (%)	*p* value
Infant Characteristics	*n* = 268 (51%)	*n* = 262 (49%)	
Gestational age at birth, mean (wks.) (mean ± SD)	30 ± 3	31 ± 3	0.08
Birth weight, mean (g) (mean ± SD)	1,481 ± 528	1,617 ± 507	0.005
Male sex	123/268 (46)	143/262 (55)	0.08
Outborn	16/267 (6)	16/261 (6)	0.95
Culture positive sepsis	12/268 (4)	10/261 (4)	0.70
Necrotizing Enterocolitis, proven	10/267 (4)	9/261 (3)	0.87
Gastrostomy Tube	23/268 (9)	17/262 (6)	0.48
Bronchopulmonary dysplasia, oxygen at 36 wk	46/267 (17)	39/260 (15)	0.50
Discharge weight, mean (g) (mean ± SD)	2,797 ± 926	2,757 ± 820	0.54
Length of stay in NICU, mean (days) (mean ± SD)	52 ± 43	46 ± 38	0.10
Any Human Milk at Discharge	170/268 (63)	186/262 (71)	0.07
Private Insurance	93/121 (77)	119/136 (88)	0.03
Public Insurance	77/147 (52)	67/126 (53)	0.86

Discussion

In this study, we report on the provision of MOM, comparing pre-pandemic and pandemic time periods for preterm infants discharged from the NICU. There was no association found between provision of MOM and the COVID-19 pandemic for the total cohort of preterm mother-infant dyads. However, after adjusting for covariates that predict MOM provision, a strong association was noted between private insurance and increased provision of MOM. These findings highlight a disparity between insurance types, especially as it relates to changes during the COVID-19 pandemic.

For our total cohort, maternal and infant characteristics and medical complications were similar between time periods, except for a few differences. There were more mothers with a clinical diagnosis of chorioamnionitis during the pandemic period. This finding is similar to the reports of other investigators. In a Canadian cohort, authors reported a 1.24 increased risk of clinical chorioamnionitis during the COVID-19 lockdown period compared to a corresponding 2015–2019 period (18). Despite the significant group difference identified in our data set, clinical chorioamnionitis did not have an impact on our primary outcome. However, several maternal medical complications during pregnancy that prevent early NICU visitation could potentially delay the initiation of expressing breast milk. In contrast, factors that enhance breast feeding, such as kangaroo care, could be explored further in the setting of pandemics (19).

An additional finding for our cohort was mothers were more likely to report being single during the pandemic. This may be related to COVID-19 isolation and social distancing guidelines, as marriages were often postponed during the

TABLE 3 Logistic regressions of maternal & infant characteristics to predict MOM at discharge for the entire study period.

	Total Cohort *n* = 509	*p* value	Public *n* = 261	*p* value	Private *n* = 248	*p* value
	aOR (95% CI)		aOR (95% CI)		aOR (95% CI)	
Born during the pandemic	1.3 (0.84–1.95)	0.26	0.95 (0.5–1.7)	0.86	2.02 (1.02–3.97)	0.04
Maternal age, years	1.02 (0.98–1.06)	0.3	1.05 (1.0–1.1)	0.06	0.96 (0.9–1.0)	0.3
Public Insurance	0.31 (0.19–0.50)	0.0001	N/A	N/A	N/A	N/A
Single	0.7 (0.4–1.2)	0.17	0.95 (0.5–1.7)	0.87	0.4 (0.2–0.99)	0.048
Non-White Race	1.1 (0.71–1.71)	0.67	1.25 (0.7–2.1)	0.42	0.78 (0.4–1.7)	0.52
Less than HS graduate	0.5 (0.2–0.9)	0.03	0.4 (0.2–0.99)	0.047	0.4 (0.8–2.6)	0.37
Length of NICU Stay, 10 days	0.87 (0.83–0.91)	0.0001	0.82 (0.8–0.9)	0.0001	0.91 (0.84–0.98)	0.02

pandemic (20). In our private insurance regression model, single status was associated with decreased odds of MOM provision at discharge. This finding may be partially explained by the importance of partner support for lactating mothers, particularly in times of overwhelming pandemic-related stress.

Another difference seen between time periods was infant birth weight, infants born during the pandemic were larger. There are conflicting reports on birthweight in pre-pandemic vs. pandemic time periods (21, 22). The magnitude of the difference decreased, though significance was retained when adjusting for GA. These findings may be a reflection that fewer infants were born at younger GA during the pandemic time period; the mean GA was one week greater in the pandemic time period. Although we interpret this finding with caution as GA differences were not statistically significant, Alshaikh et al. also report that GA and birth weight were higher in infants admitted to the NICU during the lockdown period (18).

While provision of MOM was similar between time periods, it was not until we explored rates by insurance type that clear group differences were identified. There was a significant increase in MOM for the private insurance group. A recent United Kingdom study by Hamid et al. that assessed poverty utilizing an index of multiple deprivation index (IMD) found similar results. Specifically that during the pandemic, women in the higher IMD (least deprived) quintiles were 2–4 times more likely to be feeding breast milk at NICU discharge than those in lower quintiles (23). It is possible that the mothers with private insurance have more opportunities to be present in the NICU, subsequently leading to increased exposure to supportive services and environments. Kelleher et al. reported patients with private insurance were able to spend more hours at the bedside per visit (5.7 h vs. 3.5 h), and an average of one more day per week in the NICU than patients with public insurance (24). Services such as in person lactation support, opportunities for skin-to-skin, participation in bedside care, and collaboration with the medical care team all facilitate successful breast milk production (25, 26). However, careful attention to not only the availability, but the accessibility of such services and opportunities for all groups of mothers is critical.

It was encouraging that provision of MOM did not significantly decrease for our mothers with public insurance. This may be a testament to mother's resiliency. Challenges that low-income mothers with public insurance may have faced during the pandemic include limited time off from work-place responsibilities, particularly if they were frontline or essential workers. In the United States, many essential workers, including those employed in public transit, nursing homes and food manufacturing plants, are reliant on public insurance (27, 28). Additional potential barriers low-income families may have encountered include limited access to transportation to the hospital, or problems finding care for children at home. NICU families with transportation difficulties are known to have decreased breast milk use at discharge (8). While data on maternal job status, available transportation, and home child care were not available for this cohort, they all relate to health care disparities and should be considered when supporting families of high-risk neonates.

Prolonged hospital stays provided a significant negative impact on MOM provision at discharge for our total cohort and separately for both insurance groups, which is not surprising as length of stay is a known risk factor for decreased MOM provision (29). One difficulty with maintaining breast milk provision is the amount of time needed for milk expression prior to each feed. For infants with prolonged hospital stay, mothers may need to return to work, challenging the ability to adequately express milk. Type of work has also been shown to have an impact on sustained provision of MOM which could relate to insurance status (30). Mothers in service/labor occupations have been reported to have the shortest breastfeeding duration (5.9 months average duration) as compared to non-working mothers or those in professional/managerial occupations (7.3–7.4 months average duration) (30). As longer hospital stays are correlated with illness severity among preterm infants, addressing disparities is critical.

Strengths and limitations

Strengths of the study include a large cohort of high-risk preterm infants. To our knowledge, this is the first study in the United States to examine associations between the pandemic and provision of MOM for preterm infants and the differential effects of insurance type. Findings from our study are timely, as several pandemic-related policies are still in effect at hospitals, and may provide opportunity for modifications if needed. We recognize the limitations of this study, including the lack of data pertaining to confounders such as parental visitation, time spent with lactation team, and quantity of MOM available at discharge. Additionally, we did not collect data on maternal COVID positivity status, which may have impacted mother's ability to visit her neonate, and provide breast milk.

Conclusion

Regression analysis of our total cohort identified the importance of the contribution of public health insurance to our outcome of MOM provision. In the separate adjusted regressions by insurance, rates of MOM provision for mothers with public insurance remained unchanged during the two time periods, whereas mothers with private insurance were

twice as likely to provide MOM during the pandemic. In summary, during the pandemic, type of health insurance impacted on provision of MOM. The study findings can be leveraged to support the need for hospitals to continually monitor and evaluate outcomes to ensure equal and equitable opportunity for all families.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to Lauren Boudreau, *lboudreau@wihri.org*.

Author contributions

LB: conceptualized and designed the study, identified variables for data collection, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. BV and EM: designed the study, identified variables for data collection, and critically reviewed the manuscript for important intellectual content. RT: coordinated and supervised data collection, carried out data analysis, and reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Are preterm birth and very low birth weight rates altered in the early COVID (2020) SARS-CoV-2 era?

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Objective: We evaluated the prevalence of preterm birth (PTB) and very low birth weight (VLBW) during Jan-Dec 2,020 (early COVID era) at 5 hospitals (2 in West Virginia, 3 in California) compared to Jan 2017–Dec 2019 (pre-COVID) inclusive of 2 regional perinatal centers (1 in Huntington, WV and 1 in San Jose, CA) and 3 community hospitals (1 each in Cabell, Los Angeles and Santa Clara counties).

Design/methods: We examined PTB and VLBW rates of live births at 5 US hospitals from Jan 2017–Dec 2020. We compared PTB and VLBW rates in 2020 to 2017–2019 using Poisson regression and rate ratio with a 95% confidence interval. We stratified live births by gestational age (GA) (<37, 33–36, and <33 weeks) and birth weight (≤1,500 g, >1,001 g to ≤1,500 g, ≤1,000 g). We examined PTB rates at 4 of the hospitals during Jan-Dec 2020 and compared them to the prior period of Jan 2017–Dec 2019 using Statistical Process Control (SPC) for quarterly data.

Results: We examined PTB and VLBW rates in 34,599 consecutive live births born Jan 2017–Dec 2019 to rates of 9,691 consecutive live births in 2020. There was no significant change in PTB (<37 weeks GA) rate, 10.6% in 2017–2019 vs. 11.0% in 2020 ($p = 0.222$). Additionally, there was no significant change when comparing VLBW rates in 2017–2019 to 2020, 1.4% in 2017–2019 vs. 1.5% in 2020 ($p = 0.832$).

Conclusion: We found no significant change in the rates of PTB or VLBW when combining the live birth data of 5 US hospitals in 3 different counties.

KEYWORDS

SARS – CoV – 2, preterm, birth, very low birth weight, extremely low birth weight

Introduction

Early in the SARS-CoV-2 pandemic, regional preterm birth (PTB) prevalence of very low birth weight (VLBW) infants in a designated Irish region reported temporal reduction from ~8 to ~2/1,000 live births (1). A similar reduction in extremely PTB from 2.19/1,000 to 0.19/1,000 during the nationwide lockdown was shown in a Danish study of live born singletons (2). Additionally, preterm birth rates of liveborn singletons born at 32–36 week GA were notably decreased following the lockdown implementation in China during Feb-May 2020 (3). In contrast, a pregnancy cohort of all births in two hospitals in Philadelphia did not show significant changes in singleton preterm or stillbirth rates (4). Stillbirths were no different in England either (5). Ten of the first twenty SARS-CoV-2 U.S. cases were reported in California (6) while West Virginia was the last US state to report the virus, several weeks after the first report on the West Coast. Our aim was to assess the PTB and VLBW rates of all live births at five US hospitals during the COVID-19 pandemic, including centers in California and West Virginia, to be representative of temporal variation in spread of the virus and all major racial, ethnic, and sociodemographic groups. Of note, all 3 US regions had undergone hospital bankruptcies, mergers and acquisitions during our study period.

Methods

We examined PTB and VLBW rates of live births at five US hospitals, two in West Virginia and three in California, from Jan 2017 to Dec 2020. We compared PTB and VLBW rates in 2020 to 2017–2019 using Poisson regression and rate ratio with a 95% confidence interval. We stratified live births by gestational age (GA) (<37, 33–36, and <33 weeks) and birth weight (≤1,500 g, >1,001g to ≤1,500 g, ≤1,000 g). We examined PTB rates at four of the hospitals during Jan-Dec 2020 and compared them to prior period of Jan 2017–Dec 2019 using Statistical Process Control (SPC) for quarterly data.

Results

We examined PTB and VLBW rates in 34,599 consecutive live births born Jan 2017–Dec 2019 to the rates of 9,691 consecutive live births in 2020. **Table 1** compares PTB rates of 34,599 consecutive live births in 2017–2019 to 9,691 live births in 2020. There was no significant change in PTB (<37 weeks GA) rate, 10.6% in 2017–2019 vs. 11.0% in 2020 ($p = 0.222$). There was no difference in the subcategories of gestational age <33 or 33–36 weeks in any of the centers. **Table 2** compares VLBW rates in 2017–2019 to 2020 and shows no significant change, 1.4% in 2017–2019 vs. 1.5% in 2020 ($p = 0.832$). There was no difference in the subcategories of birth weight 1,000–1,500 or ≤1,000 g in any of the centers except the regional NICU in San Jose, California showed an increase in ELBW (≤1,000 g) from 0.4% in 2017–2019 to 0.8% in 2020 ($p = 0.013$). **Figures 1**, **2** illustrate the quarterly birth rates in the birth weight and gestational age categories. The preterm birth rate in 2020 first quarter was an outlier due to an increase in the 33–36 weeks gestational age subcategory, although the subsequent rates are stable within the control limits. There are no outliers or significant shift in the overall birth rates in the gestational age or birth weight categories. The racial and ethnic distributions of all live births examined are as follows: 53% Hispanic, 30% Caucasian, 8% African American, 8% Asian, and 1% Other (data not presented).

Discussion

In the first year of the pandemic, 2020, we did not find a significant change in the rates of PTB or VLBW when combining the live birth data of five US hospitals in two different states and three different regions. No decrease in PTB or VLBW rates were noted at any of the five hospitals examined.

Similar results are noted in a study from France seeking to examine effect of lockdowns in perinatal outcomes in 2020, showing neither differences in preterm, nor stillbirth rates, nor LBW and adjusted VLBW rates in their cohort (7). In addition, preterm birth rates were reported unchanged in a large hospital system in Boston, MA in the USA during the first peak of the pandemic era (April-July 2020), secondary findings included no difference in spontaneous verse iatrogenic preterm birth rates (8). A more recent study from Australia showed decline in births <34 weeks GA during 2020–21 lockdowns but without significant change for births <28 weeks GA (9). A consortium of European nations, report decline in live birth rates, some with a subsequent rebound in early 2021 and excess COVID mortality as a putative reason for declining live births (10, 11). Recent (2020–21) Canadian surveillance data suggest increased preterm birth risk among 6,012 SARS-CoV-2–affected pregnancies (11.05% vs. 6.76%; relative risk, 1.63 [95% CI, 1.52–1.76]), inclusive of milder disease not requiring hospitalization, compared to unaffected contemporaneous pregnancies (12). A study from Bronx, New York, found preterm birth rates to be altered by the SARS-CoV-2 variant in women testing positive for SARS-CoV-2 during pregnancy (13). The rates of PTB were found to be lower during the Omicron variant surge when compared to the PTB rates during the original strain surge (13). These findings were attributed to differing variant virulence, increased vaccination availability, and improved SARS-CoV-2 management guidelines amongst other factors (13).

TABLE 1 Comparison of pre-COVID era (2017–2019) vs. COVID era (2020) preterm birth rates across five medical centers stratified by gestational age (GA).

Center	GA, weeks	Year	*n*	Rate	Rate Ratio (95% CI)	*p* value
All centers[a] (2017–19 $N = 34,599$; 2020 $N = 9,691$)	<37	2017–19	3,658	10.6% (10.2, 10.9)	0.96 (0.90, 1.03)	0.222
		2020	1,069	11.0% (10.4, 11.7)		
All centers (excluding St Francis Medical center)[b] (2017–19 $N = 21,955$; 2020 $N = 6,648$)	<37	2017–19	2,476	11.3% (10.8, 11.7)	0.94 (0.87, 1.02)	0.160
		2020	794	11.9% (11.1, 12.8)		
	33–36	2017–19	1,917	8.7% (8.3, 9.1)	0.92 (0.84, 1.01)	0.075
		2020	630	9.5% (8.8, 10.2)		
	≤32	2017–19	534	2.4% (2.2, 2.6)	0.99 (0.83, 1.17)	0.874
		2020	164	2.5% (2.1, 2.9)		
Santa Clara Valley Medical Center San Jose, California (2017–19 $N = 8,926$; 2020 $N = 2,780$)	<37	2017–19	773	8.7% (8.1, 9.3)	0.91 (0.79, 1.05)	0.196
		2020	264	9.5% (8.4, 10.7)		
	33–36	2017–19	632	7.1% (6.5, 7.7)	0.94 (0.80, 1.10)	0.416
		2020	210	7.6% (6.6, 8.6)		
	≤32	2017–19	141	1.6% (1.3, 1.9)	0.81 (0.59, 1.11)	0.196
		2020	54	1.9% (1.5, 2.5)		
O'Connor Hospital San Jose, California (2017–19 $N = 4,085$; 2020 $N = 950$)	<37	2017–19	340	8.3% (7.5, 9.3)	0.98 (0.77, 1.24)	0.845
		2020	81	8.5% (6.9, 10.6)		
	33–36	2017–19	275	6.7% (6.0, 7.6)	0.93 (0.71, 1.21)	0.573
		2020	69	7.3% (5.7, 9.2)		
	≤32	2017–19	40	1.0% (0.7, 1.3)	0.78 (0.41, 1.48)	0.439
		2020	12	1.3% (0.7, 2.2)		
Cabell Huntington Hospital Huntington, West Virginia (2017–19 $N = 7,849$; 2020 $N = 2,604$)	<37	2017–19	1,327	16.9% (16.0, 17.8)	1.00 (0.90, 1.11)	0.992
		2020	440	16.9% (15.4, 18.6)		
	33–36	2017–19	974	12.4% (11.7, 13.2)	0.94 (0.84, 1.07)	0.367
		2020	342	13.1% (11.8, 14.6)		
	≤32	2017–19	353	4.5% (4.1, 5.0)	1.20 (0.96, 1.49)	0.119
		2020	98	3.8% (3.1, 4.6)		
St Mary's Medical Center[c] Huntington, West Virginia (2017–19 $N = 1,095$; 2020 $N = 314$)	<37	2017–19	36	3.3% (2.4, 4.6)	1.15 (0.55, 2.38)	0.713
		2020	9	2.9% (1.5, 5.5)		
	33–36	2017–19	36	3.3% (2.4, 4.6)	1.15 (0.55, 2.38)	0.713
		2020	9	2.9% (1.5, 5.5)		
	≤32	2017–19	0			
		2020	0			
St Francis Medical Center[d] Los Angeles, California (2017–19 $N = 12,644$; 2020 $N = 3,043$)	<37	2017–19	1,182	11.3% (10.8, 11.7)	0.94 (0.87, 1.02)	0.16
		2020	275	11.9% (11.1, 12.8)		

[a]Combined data for all centers could only be described as GA <37 weeks because St Francis Medical Center did not provide stratified GA data.
[b]St Francis Medical Center data did not provide stratified GA data thus was not included combined estimates.
[c]St Mary's Medical Center does not care for infants <32 weeks GA, hence no data available for that GA group.
[d]St Francis Medical Center provided GA data ranging between 22 and 36 weeks GA but there was insufficient data available to be able to stratify the GA.

TABLE 2 Comparison of pre-COVID era (2017–2019) vs. COVID era (2020) low birth weight rates across five medical centers stratified by birth weight.

Center	Birth weight, g	Year	*n*	Rate	Rate Ratio (95% CI)	*p* value
All centers (excluding St Mary's Medical center)[a] (2017–19 *N* = 33,504; 2020 *N* = 9,377)	≤1,500	2017–19	476	1.4% (1.3, 1.6)	0.98 (0.81, 1.19)	0.832
		2020	136	1.5% (1.2, 1.7)		
	>1,000 and ≤1,500	2017–19	297	0.9% (0.8, 1.0)	1.15 (0.89, 1.49)	0.274
		2020	72	0.8% (0.6, 1.0)		
	≤1,000	2017–19	179	0.7% (0.5, 0.9)	0.78 (0.59, 1.04)	0.093
		2020	64	0.5% (0.5, 0.6)		
Santa Clara Valley Medical Center San Jose, California (2017–19 *N* = 8,926; 2020 *N* = 2,780)	≤1,500	2017–19	92	1.0% (0.8, 1.3)	0.73 (0.51, 1.07)	0.107
		2020	39	1.4% (1.0, 1.9)		
	>1,000 and ≤1,500	2017–19	56	0.6% (0.5, 0.8)	1.03 (0.60, 1.77)	0.926
		2020	17	0.6% (0.4, 1.0)		
	≤1,000	2017–19	36	0.4% (0.3, 0.6)	0.51 (0.30, 0.87)	0.013
		2020	22	0.8% (0.5, 1.2)		
O'Connor Hospital San Jose, California (2017–19 *N* = 4,085; 2020 *N* = 950)	≤1,500	2017–19	14	0.3% (0.2, 0.6)	1.09 (0.31, 3.78)	0.898
		2020	3	0.3% (0.1, 1.0)		
	>1,000 and ≤1,500	2017–19	10	0.2% (0.1, 0.5)	1.16 (0.25, 5.31)	0.846
		2020	2	0.2% (0.1, 0.8)		
	≤1,000	2017–19	4	0.1% (0.0, 0.3)	0.93 (0.10, 8.32)	0.948
		2020	1	0.1% (0.0, 0.7)		
Cabell Huntington Hospital Huntington, West Virginia (2017–19 *N* = 7,849; 2020 *N* = 2,604)	≤1,500	2017–19	240	3.1% (2.7, 3.5)	1.21 (0.92, 1.58)	0.177
		2020	66	2.5% (2.0, 3.2)		
	>1,000 and ≤1,500	2017–19	150	1.9% (1.6, 2.2)	1.38 (0.96, 1.99)	0.081
		2020	36	1.4% (1.0, 1.9)		
	≤1,000	2017–19	90	1.1% (0.9, 1.4)	1.00 (0.66, 1.50)	0.982
		2020	30	1.2% (0.8, 1.6)		
St Francis Medical Center Los Angeles, California (2017–19 *N* = 12,644; 2020 *N* = 3,043)	≤1,500	2017–19	130	1.0% (0.9, 1.2)	1.12 (0.74, 1.68)	0.594
		2020	28	0.9% (0.6, 1.3)		
	>1,000 and ≤1,500	2017–19	81	0.6% (0.3, 0.9)	1.15 (0.68, 1.93)	0.608
		2020	17	0.6% (0.3, 0.9)		
	≤1,000	2017–19	49	0.4% (0.3, 0.5)	1.07 (0.56, 2.06)	0.835
		2020	11	0.4% (0.2, 0.7)		

[a]St Mary's Medical Center data did not provide birth weight-based data thus was not included combined estimates.

There was a significant increase in ELBWs in the San Jose regional hospital which was likely related to the change in referral patterns of high risk deliveries across the local county rather than the pandemic. The county acquired two community hospitals in early 2019 and the referral pattern for high-risk mothers were streamlined to deliver at the regional center. In addition, there was a local closure of the Labor and Delivery service at another community center that also redirected high risk mothers to the regional center.

As detailed above, multiple studies have been performed to analyze the effects of the COVID19 pandemic on perinatal outcomes and have shown conflicting results. A large rapid review and meta-analysis by Vaccaro et. al., was performed to examine the impact of the COVID-19 lockdown on the incidence of preterm birth, low birth weight, and stillbirth during the lockdown measures (14). When combining the data of 14 previous studies, the meta-analysis showed a significant risk of stillbirth during the COVID-19 lockdown

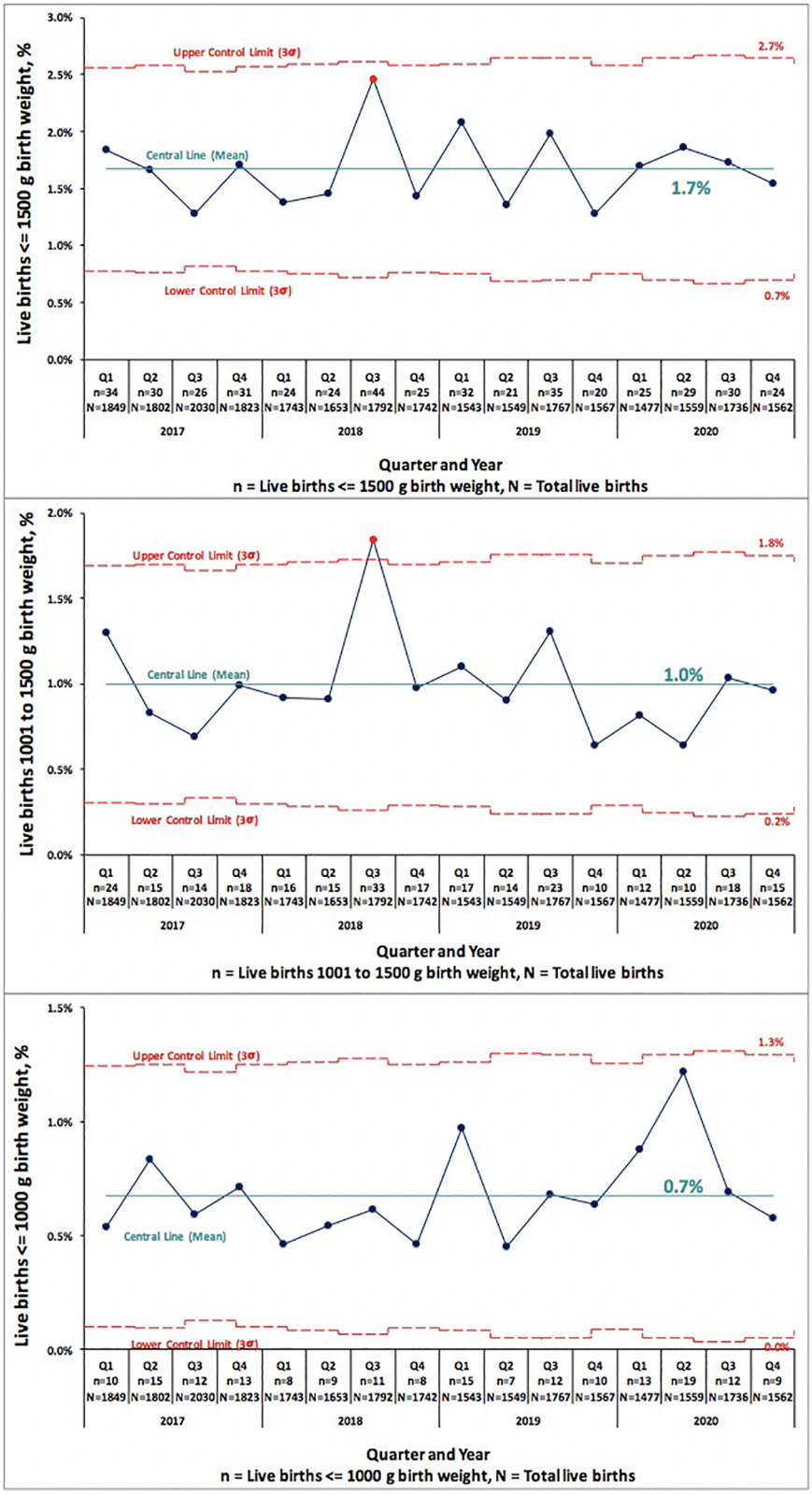

FIGURE 1
Pre-COVID-19 era (2017–2019) and COVID-19 era (2020) birth rates across five medical centers stratified by gestational age shown as statistical process control "p" chart. The central line represents mean and the upper and lower control limit lines are three standard deviations above and below mean.

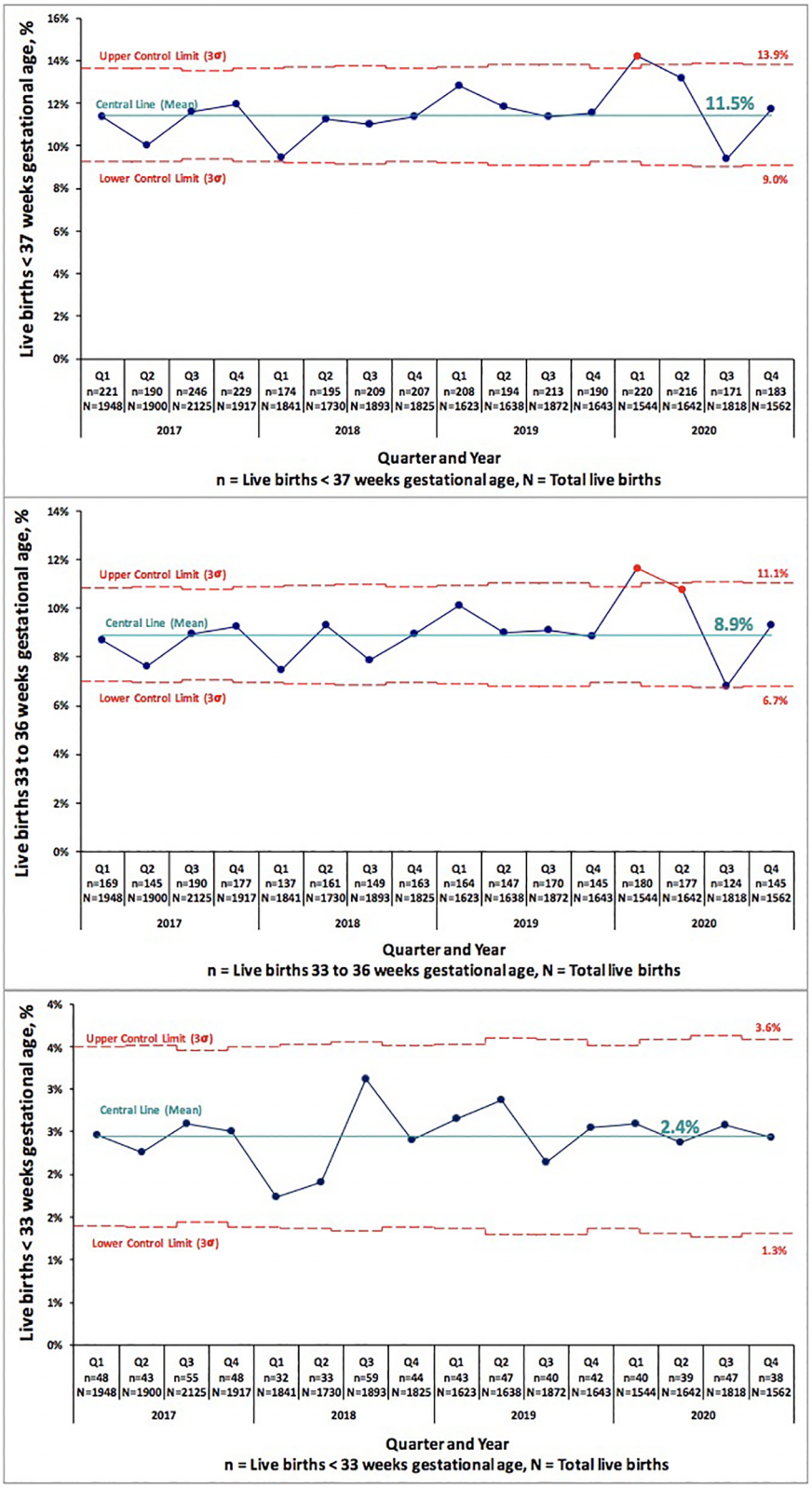

FIGURE 2
Pre-COVID-19 era (2017–2019) and COVID-19 era (2020) birth rates across five medical centers stratified by birth weight shown as statistical process control "p" chart. The central line represents mean and the upper and lower control limit lines are three standard deviations above and below mean.

when compared to the prepandemic period (14). However, PTB, LBW, and VLBW were not associated with a significant risk during the lockdown period (14).

Strengths of our study include a longer period of observation of all pregnancies into the early COVID era, a robust sample size with geographic, racial and ethnic heterogeneity. Limitations of our observations include lack of stillbirth data and inability to distinguish spontaneous vs. medically indicated preterm birth. Further limitations of our study include completing our study in 2020 thus lacking accurate SARS-CoV-2 infection rates and possibly largely excluding impact of vaccines and differing SARS-CoV-2 variants in pregnant women. In addition, local factors such as changes in referral patterns related to bankruptcies, mergers and acquisitions cannot be excluded.

Conclusion

We conclude that in the first COVID-era year studied, 2020, SARS-CoV-2 did not reduce preterm or low birth weight rates in three different regions in the United States when combining the birth data of five US hospitals, compared to live births 2017–2019 at these same institutions. Local, regional and population-wide studies show variation in impact in SARS-CoV-2 on preterm birth rates, due to multitude of dynamic factors. These will have implications for planning and delivery of regionalized perinatal health care systems.

Data availability statement

The original contributions presented in the study are included in the article/further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

KR, MN, PJ, KD, SN, RP and BG conceptualized and designed the study. Data collection by AH, JH, RC, KF, MC, MS. MN, AH and JH responsible for SPC and data analysis. All authors contributed to data interpretation and manuscript writing and approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Examination of cord blood at birth in women with SARS-CoV-2 exposure and/or vaccination during pregnancy and relationship to fetal complete blood count, cortisol, ferritin, vitamin D, and CRP

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Background: SARS-CoV-2 is known to manifest a robust innate immune response. However, little is known about inflammatory influences from maternal SARS-CoV-2 infection or maternal mRNA vaccination upon the fetus. In addition, it is unknown if Vitamin D deficiency influences fetal homeostasis or if an anti-inflammatory mechanism to the development of possible innate cytokines or acute phase reactants by the maternal/fetal dyad, in the form of cortisol elevations, occur. In addition, effects on Complete Blood Count (CBC) are not known.
Objective: To evaluate the neonatal acute phase reactants and anti-inflammatory responses after maternal SARS-CoV-2 disease or mRNA vaccination.
Methods: Samples and medical records reviews from mother/baby dyads ($n = 97$) were collected consecutively, and were categorized into 4 groups; no SARS-CoV-2 or vaccination exposure (Control), Vaccinated mothers, maternal SARS-CoV-2 disease positive/IgG titer positive fetal blood, and maternal SARS-CoV-2 positive/IgG titer negative fetal blood. SARS-CoV-2 IgG/IgM/IgA titers, CBC, CRP, ferritin, cortisol, and Vitamin D were obtained to examine the possible development of an innate immune response and possible anti-inflammatory response. Student's *t*-test, Wilcoxon rank-sum, and Chi-squared with Bonferroni corrections were used to compare groups. Multiple imputations were performed for missing data.
Results: Cortisol was higher in babies of both mothers who were vaccinated ($p = 0.001$) and SARS-CoV-2 positive/IgG positive ($p = 0.009$) as compared to the control group suggesting an attempt to maintain homeostasis in these groups. Measurements of ferritin, CRP, and vitamin D did not reach statistical significance. CBC showed no variation, except for the mean platelet volume (MPV), which was elevated in babies whose mothers were vaccinated ($p = 0.003$) and SARS-CoV-2 positive/IgG positive ($p = 0.007$) as compared to the control group.

Conclusion: Acute phase reactant elevations were not noted in our neonates. Vitamin D levels were unchanged from homeostatic levels. Cord blood at birth, showed Cortisol and MPV higher in vaccinated and SARS-CoV-2 IgG positive mother/baby dyads as compared to the Control group, indicating that possible anti-inflammatory response was generated. The implication of possible inflammatory events and subsequent cortisol and/or MPV elevation effects upon the fetus after SARS-CoV-2 disease or vaccination is unknown and merits further investigation.

KEYWORDS

SARS-CoV-2, vaccines, cord blood, acute phase reactants, IL-6, cortisol, ferritin, vitamin D

1. Introduction

Current maternal-fetal research into SARS-CoV-2 (COVID-19) disease has centered upon the presence or absence of vertical disease transmission and passive transfer of maternal IgG in both naturally infected and vaccinated mothers (1). Vertical transmission of COVID-19 has been found to be rare (1, 2). This is thought to be related to the significantly low number of ACE2 viral binding receptors in the placenta (1, 3). To date, the innate immune system has been determined to be a significant part of the human response to SARS-CoV2 infection. It is known that SARS-CoV-2 is a highly inflammatory disease with significant elevations in innate cytokines such as IL-1, TNFα, and IL-6, all released by macrophages following induction of the complement cascade (4–6). These cytokines are associated with acute phase reactant development of mediators such as ferritin and CRP, which are released from the liver (6). Elevations in acute phase reactants have been noted in adults and children with severe COVID-19 infection (7, 8). Recent work has focused on the effects of the maternal innate immune response to COVID-19 and the placental response to maternal infection (9).

Protection from COVID-19 infection is an important part of prenatal care. Neonates must rely on both innate immune responses such as cytokine interferon type 1, which has anti-viral properties, the success of maternal defeat of the infection, and maternally acquired transplacental antibodies for protection from disease (10). Multiple studies conclude maternal immunization results in higher, longer-lasting SARS-CoV-2 IgG levels in neonates (11–13). Additionally, it has been shown that maternal immunization also yields immunoglobulin protection in breast milk, specifically IgA (12, 13). This research has given obstetric providers the evidence to further encourage their patients to obtain COVID-19 immunizations as well as remain up to date with boosters (14). During the pandemic, the mRNA vaccines demonstrated protection against the spike protein of COVID-19 (15). In contrast, native disease will generate IgG antibodies to both the spike protein and the nucleocapsid of the virus (15). Passive transfer of maternally derived COVID-19 specific IgG antibody begins 2 weeks after vaccination (13). COVID-19-specific IgG transference from native COVID-19 is more time-dependent, with the highest neonatal titers developed during second-trimester infections as compared to more recent infection during the third trimester (12, 16). The mRNA vaccine mechanism has been studied and generates a facilitated immune response by complement cascade activation acting as the adjuvant to the vaccine (17). Initiation of the complement cascade by either infection or vaccination may have implications on downstream markers of inflammation and the generation of acute phase reactants (18).

With the activation of inflammation and stress, it is likely the mother may mount an anti-inflammatory response to resolve these influences during both infection and vaccination. The neonate also possesses several hormones to affect immune homeostasis if influenced by infection or maternal immune responses. Vitamin D and cortisol are the predominate hormones helping to maintain neonatal anti-inflammatory stance and reestablishing homeostasis. Vitamin D is frequently placental in origin, and cortisol levels in the mother are known to be partially placentally transferred to the fetus (19–21). In addition, stressors of either the mother, neonatal infection, or the birthing process itself may also cause the neonate to generate cortisol on its own (22, 23). This suggests that the bi-directional effect within the maternal/fetal dyad on cortisol has a vital role in the maintenance of neonatal homeostasis.

We hypothesize that innate immune response in both vaccination and COVID-19 disease may increase neonatal exposure to innate cytokines, yielding an inflammatory response by generation of acute phase reactants with associated homeostatic generation of anti-inflammatory elevation of cortisol and Vitamin D levels. In this study, we will assess this hypothesis by evaluating cord blood acute phase reactants ferritin and CRP and any inflammatory influence on the CBC. In addition, we will test whether a corresponding compensatory elevation in cord blood anti-inflammatory hormones of cortisol and Vitamin D in the setting of maternal COVID-19 disease or post-immunization is found.

2. Methods

This prospective cohort study sought to collect cord blood samples with either documented maternal SARS-CoV-2 exposure and/or vaccination in pregnancy or mothers who lacked prior SARS-CoV-2 exposure and/or vaccination in pregnancy, however only 97 were found to meet our inclusion criteria during our period of sample collection. Samples were collected consecutively, at Cabell Huntington Hospital's labor and delivery department in Huntington, West Virginia, United States, followed by medical

chart reviews of the mother and neonate charts to extract all pertinent data. Exclusion criteria were mothers who were transferred from an outside facility, infants born with congenital defects or disease, any mother/infant dyad who was missing critical information for our dataset, and any mother/infant dyad whose placenta didn't yield enough cord blood for testing. Additional inclusion criteria included neonates delivered after 32 weeks gestational age to ensure transference of immunoglobulins. Dyads that failed screening for technical reasons (gestational age less than 32 weeks) or arrival of the research team in an insufficient time to collect blood due to expected clotting of fetal vessels were not recorded. One-hundred-six samples were collected, and the resulting 97 samples from the cohort of mother/baby dyads were divided into four groups; Control: SARS-CoV-2 negative mothers with no history of vaccination and SARS-CoV-2 IgG negative fetal blood; Vaccinated: vaccinated mothers/IgG positive fetal blood. Unvaccinated/SARS-CoV-2(+)/IgG(+): non-vaccinated SARS-CoV-2 positive/IgG positive fetal blood; Unvaccinated/SARS-CoV-2(+)/IgG(−): non-vaccinated SARS-CoV-2 positive/IgG negative fetal blood. Maternal and neonatal demographics, including birthweights and clinical variables were obtained from a medical records review. A minimum of 6 cc umbilical cord blood was obtained in the first few (typically <10) minutes after placental delivery. A portion of serum from the fetal blood was sent to Cincinnati Children's Hospital Nephrology Lab, Cincinnati, Ohio, United States, for analysis of SARS-CoV-2 specific IgG, IgM, and IgA antibody titers. SARS-CoV-2 specific IgA was obtained to exclude the possibility of maternal blood contamination, as immunologically, the neonate cannot generate IgA immunoglobulin until 2–3 weeks after birth; at the same time, these IgA levels are amply found in the maternal bloodstream (24, 25). CBC, CRP, ferritin, cortisol, and Vitamin D were measured in the cord blood at Cabell Huntington Hospital. Informed consent was not required for this study as cord blood samples were obtained by forfeited placental/cord blood specimens, and maternal/fetal demographics were obtained by medical chart review and de-identified. This research study was approved by the Marshall University Medical Internal Review Board (IRB), IRB# 1726140, prior to its initiation.

2.1. Statistical analysis

Descriptive statistics were used to characterize infant and maternal metrics. Mean (standard deviation), and median (25th, 75th interquartile) were used for parametric and non-parametric data, respectively. The Modified Levene's test was used to compare the variance of continuous data between study groups. Student's *t*-test and Welch's *t*-test were used for comparing parametric continuous data between study groups. The Wilcoxon rank-sum test was used to compare non-parametric continuous data between study groups. Pearson's chi-squared test and Fisher's exact test were used for comparing proportional differences in categorical data between study groups. Bonferroni correction was conservatively applied for all multiple comparisons; hence, we considered statistical significance to be a p-value < 0.0167. Multiple imputations, using univariate interval regression models, were used for missing CBC data that were missing completely at random (MCAR). Data were evaluated for any gross deviations from statistical testing assumptions.

3. Results

A total of 106 cord blood samples were collected from May 2021 to August 2022 after placental delivery. Nine samples were excluded due to missing data, which prevented them from being assigned to a study group. The final study population included 97 samples that were divided into four groups based on maternal SARS-CoV-2 exposure/vaccination and the presence or absence of neonatal SARS-CoV-2 specific IgG.

All vaccinated mothers received mRNA vaccine as they were the only regionally available vaccines during the period of study collection. Vaccination and SARS-CoV-2 exposure data are included in **Table 1**. Differences in maternal and neonatal demographics were noted between groups (**Tables 2**, **3**). Birth complications were lower in the Unvaccinated/SARS-CoV-2 (+)/IgG(+) group compared to the Control group (20% vs. 60%, $p = 0.005$). Respiratory distress syndrome (RDS) was lower in the Unvaccinated/SARS-CoV-2(+)/IgG(+) group compared to the Control group (3% vs. 27%, $p = 0.024$). Neonatal abstinence syndrome (NAS) was lower in the Unvaccinated/SARS-CoV-2 (+)/IgG(+) group compared to the Control group (0% vs. 20%, $p = 0.023$). In addition, a greater proportion of vaccinated mothers intended to exclusively breastfeed compared to unvaccinated mothers (Control) (83% vs. 53% $p = 0.001$).

Differences in infant immunological titers were noted between groups (**Table 4**). The groups containing Vaccinated and early-in-pregnancy COVID-19 disease (greater than 2 weeks prior to delivery) had IgG titers to SARS-CoV-2 (**Table 4**). All mothers assigned to the Control group by history also had no evidence of IgG-specific COVID-19 in fetal blood, to exclude the possibility of asymptomatic disease. Most, 27 of the 32 cord blood samples (84%) in the Vaccinated group showed SARS-CoV-2 specific IgG titers above our reference laboratory's upper limit of detection (1:12,800). Eleven of the 32 vaccinated mothers (34%) also had a history of SARS-CoV-2 disease. All 11 of these mothers (100%) showed SARS-CoV-2 specific IgG titers above our upper limit of detection (1:12,800). All mothers who had COVID-19 disease within 2 weeks (Unvaccinated/Sars-CoV2(+)/IgG(−)) prior to delivery did not transfer IgG COVID-19 specific antibody to their neonates (**Table 4**). Indeterminate (non-titratable) levels of SARS-CoV-2 specific IgM antibody were found in 1 sample from a Vaccinated mother. Vertical transmission and maternal blood contamination are unlikely in this sample, as the mother was vaccinated at least 2 weeks prior to delivery, and SARS-COV-2 specific IgA was undetected (**Table 4**). Fetal tissues are known to make IgM as early as 10–11 weeks of gestation (26), and this is detectable in fetal blood as early as 13 weeks of gestation (27), but reference nomograms for fetal IgMs suggestive of fetal infection exist for fetuses > 23 weeks and through term (28). Differences in infant inflammatory and anti-inflammatory

TABLE 1 Maternal vaccination and SARS-CoV2 exposure data stratified by study groups based on SARS-CoV2 exposure/vaccination and presence of neonatal SARS-Cov2 specific IgG, $N = 97$.

	Descriptive statistic	Unvaccinated SARS-CoV-2(−) SARS-CoV-2 IgG(−) [Control]	Vaccinated	Unvaccinated SARS-CoV-2(+)		*P* value		
				SARS-CoV-2 IgG (+)	SARS-CoV-2 IgG (−)	Control vs. Vaccinated	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(+)	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(−)
		$N = 15$	$N = 32$	$N = 35$	$N = 15$			
Tested positive during pregnancy[a]	*n*/*N*, (%)	0/2 (0%)	11/30 (37%)	28/28 (100%)	15/15 (100%)	.534	.002***	.007***
Vaccinated during pregnancy[a]	*n*/*N*, (%)	0/2 (0%)	32/32 (100%)	0/27 (0%)	1/14 (7%)	.002***	1.000	1.000
Fully vaccinated >=2 weeks prior to birth[a]	*n*/*N*, (%)	0/2 (0%)	30/32 (94%)	0/27 (0%)	1/14 (7%)	.011***	1.000	1.000
Vaccine						.002***	<.001***	1.000
Moderna	%	0	25	0	7			
Pfizer	%	0	34	0	0			
Unknown mRNA brand	%	0	41	0	0			
Unvaccinated	%	13	0	77	87			
Unknown if vaccinated	%	87	0	23	7			
Doses Prior to birth						.004***	1.000	1.000
0	%	13	0	77	87			
1	%	0	6	0	0			
2	%	0	91	0	7			
Unknown	%	87	3	23	7			

[a]Missing data imputed for 1 patient.
***$p < 0.0167$ (Below Bonferroni correction).

markers were noted between groups (Table 4). Cord blood ferritin was higher in Vaccinated infants compared to the Control group (182 vs. 118 ng/mL, $p = 0.033$); however, this was not statistically significant after the Bonferroni corrections (Table 4). Percent increase in cortisol was higher in infants of both the Vaccinated (100% increase, $p = 0.001$) and the Unvaccinated/SARS-CoV2(+)/IgG(+) (60% increase, $p = 0.009$) compared to the Control group (Table 4). Quantification of inflammatory measures of CBC and CRP showed normal biological variation (Table 4). No statistically significant findings were noted for the possible inflammatory measures of CBC and CRP except the MPV. While MPV was higher in both the Vaccinated (9.6 vs. 7.9 fL, $p = 0.002$) and Unvaccinated/SARS-CoV2(+)/IgG(+) (9.4 vs. 7.9 fL, $p = 0.008$) compared to the Control group, it did not rise to the level associated with a change due to inflammation (Table 4). No groups were found to have a deficiency in Vitamin D (Table 4).

4. Discussion

Inflammation generated by an innate immune system is a critical first response to COVID-19 infection and to the COVID-19 mRNA vaccination and is needed to mount an adequate antibody response to both. To maintain mother/fetal dyad immunologic homeostasis, an anti-inflammatory response can be expected. We sought to determine the influence of inflammatory or anti-inflammatory responses during or following infection of COVID-19 or with mRNA vaccination on fetal acute phase reactant development and subsequent anti-inflammatory response. All vaccinated and known infected mothers transferred anti-COVID IgG antibodies to their fetuses. We observed no statistically significant elevations to markers of inflammation with regard to CRP, Ferritin, and CBC, with the exception of an elevation of the MPV which has an unknown relevance at birth. Anti-inflammatory hormone Vitamin D remained within a normal range for fetal cord blood. We did find statistical significance in elevations of cortisol in the cord blood of vaccinated and previously infected mothers. This novel study is the first to observe that mother/fetal dyads are mounting an anti-inflammatory response *via* cortisol in the presence of COVID mRNA vaccine and disease.

Immunoglobulin transference in our study mirrors that of the current literature (11–13). IgG was transferred to 100% of the vaccinated mothers. SARS-CoV-2 specific IgG titers were significantly elevated in Vaccinated dyads, and there was a wide distribution of SARS-CoV-2 specific IgG titers in our SARS-CoV-2(+)/IgG(+) group. No mother in the Unvaccinated/SARS-CoV-2(+)/IgG(−) group (positive COVID-19 test in the 2 weeks prior to delivery) transferred COVID-19 specific antibody to their infant. This is consistent with what has already been observed in current literature regarding the robust response in immunized individuals in as little as 2 weeks after vaccination but not prior to 2 weeks (12).

TABLE 2 Maternal demographics stratified by study groups based on SARS-CoV2 exposure/vaccination and presence of neonatal SARS-Cov2 specific IgG, *N* = 97.

	Descriptive statistic	Unvaccinated SARS-CoV-2(−) SARS-CoV-2 IgG(−) [Control]	Vaccinated	Unvaccinated SARS-CoV-2(+)		Control vs. Vaccinated	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(+)	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(−)
				SARS-CoV-2 IgG(+)	SARS-CoV-2 IgG(−)			
		N = 15	*N* = 32	*N* = 35	*N* = 15			
Rural	%	13	19	29	40	1.000	.304	.215
Smoker	%	20	3	3	33	.089	.075	.682
Second hand smoke exposure[a]	n/N, (%)	3/9 (33%)	1/13 (8%)	3/12 (25%)	5/8 (63%)	.264	1.000	.347
Age at delivery, years	Mean (SD)	29 (6)	29 (5)	27 (5)	29 (6)	.708	.183	.949
Body mass index (BMI) at delivery	Mean (SD)	35 (10)	34 (6)	34 (7)	32 (6)	.527	.645	.236
State of Residence						.697	.524	.052
Kentucky	%	0	6	11	20			
Ohio	%	20	13	20	0			
West Virginia	%	80	81	69	80			
Maternal Race/ Ethnicity						1.000	.666	1.000
African American	%	7	6	0	0			
Caucaisian/White	%	93	94	94	100			
Hispanic	%	0	0	3	0			
Unknown	%	0	0	3	0			
Mom's intent to breast feed						.001***	.386	.324
Bottle fed only	%	47	3	29	33			
Breast fed only	%	53	84	66	47			
Supplemental fed (both)	%	0	13	6	20			

[a]Missing data is reflected by a denominator value that is less than the study group *N*.
***$p < 0.0167$ (Below Bonferroni correction).

TABLE 3 Neonatal demographics stratified by study groups based on SARS-CoV2 exposure/vaccination and presence of neonatal SARS-Cov2 specific IgG, *N* = 97.

	Descriptive statistic	Unvaccinated SARS-CoV-2(−) SARS-CoV-2 IgG(−) [Control]	Vaccinated	Unvaccinated SARS-CoV-2(+)		*P* value		
				SARS-CoV-2 IgG(+)	SARS-CoV-2 IgG(−)	Control vs. Vaccinated	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(+)	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(−)
		N = 15	*N* = 32	*N* = 35	*N* = 15			
Male sex	%	47	41	37	60	.696	.529	.715
Gestational age, weeks	Median (IQR)	37 (36, 38)	38 (37, 39)	38 (37, 39)	38 (34, 39)	.151	.075	.782
Birth weight, grams	Mean (SD)	2,898 (466)	3,063 (679)	3,192 (467)	2,866 (826)	.338	.050	.900
Birth length, cm	Mean (SD)	48 (2)	49 (3)	50 (2)	48 (4)	.161	.019*	.965
Birth head circumference, cm	Mean (SD)	33 (1)	33 (2)	34 (1)	33 (2)	.920	.060	.705
Birth body mass index (BMI)	Mean (SD)	12 (1)	12 (3)	13 (1)	12 (2)	.534	.390	.560

*$p < 0.050$.

COVID-19 disease results in innate cytokine production of TNFα, IL-1, and IL-6 in both adults and children (5). IL-6 and complement products such as C5a drive the production of CRP and ferritin, which are important acute phase reactants (6, 18). These innate cytokines have been associated with hyperferritinemia in severe COVID-19 disease (7). We suspect that high levels of C5a were unlikely to have crossed the placenta to affect fetal acute phase reactant production as determined by

TABLE 4 Infant inflammatory & anti-inflammatory markers, and immunological titers stratified by study groups based on SARS-CoV2 exposure/vaccination and presence of neonatal SARS-Cov2 specific IgG, *N* = 97.

	Descriptive statistic	Unvaccinated SARS-CoV-2(−) SARS-CoV-2 IgG (−) [Control]	Vaccinated	Unvaccinated SARS-CoV-2(+)		*P* value		
				SARS-CoV-2 IgG(+)	SARS-CoV-2 IgG(−)	Control vs. Vaccinated	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG(+)	Control vs. Unvaccinated SARS-CoV-2(+) SARS-CoV-2 IgG (−)
		N = 15	*N* = 32	*N* = 35	*N* = 15			
Ferritin, nmol/L	Mean (SD)	118 (82)	182 (97)	177 (223)	182 (103)	.033*	.326	.067
Cortisol, nmol/L	Median (IQR)	5 (2, 7)	10 (6, 14)	8 (5, 13)	8 (1, 19)	.001***	.009***	.118
Vitamin D, nmol/L[a]	Mean (SD)	36 (22)	33 (13)	31 (10)	36 (14)	.467	.200	.948
White blood cells, k/cmm	Mean (SD)	12.2 (5.5)	14.2 (5.8)	13.2 (4.5)	12.4 (6.2)	.264	.495	.929
Red blood cells, m/cmm	Mean (SD)	4.3 (0.6)	4.2 (0.6)	4.2 (0.5)	4.5 (0.6)	.699	.725	.233
Hemoglobin, gm/dL	Mean (SD)	16 (2)	15 (2)	15 (2)	17 (3)	.361	.418	.211
Hematocrit, %	Mean (SD)	48 (8)	47 (7)	47 (7)	52 (8)	.605	.590	.160
Platelets, k/cmm	Mean (SD)	197 (94)	255 (110)	231 (98)	243 (130)	.084	.253	.269
MCV, fL[b]	Mean (SD)	112 (8)	111 (7)	110 (6)	115 (7)	.780	.466	.258
MCH, pg[b]	Mean (SD)	37 (2)	36 (2)	36 (2)	37 (3)	.210	.174	.993
MCHC, gm/dL[b]	Median (IQR)	34 (32, 34)	33 (32, 33)	33 (32, 34)	33 (32, 34)	.115	.290	.911
RDW, %[b]	Mean (SD)	18.0 (1.3)	17.5 (1.6)	17.5 (1.1)	17.7 (1.1)	.299	.166	.572
MPV, fL[b]	Median (IQR)	7.9 (7.6, 8.4)	9.6 (8.5, 10.1)	9.4 (8.1, 10.1)	8.5 (7.7, 9.5)	.003***	.007***	.145
CRP, mg/dl						1.000	1.000	1.000
1.32	%	0	3	0	0			
<0.29	%	100	97	100	100			
COVID Specific IgM						1.000	1.000	1.000
Indeterminate	%	0	3	0	0			
Negative	%	100	97	100	100			
COVID Specific IgA						1.000	1.000	1.000
Negative	%	100	100	100	100			
COVID Specific IgG						<.001***	<.001***	1.000
Indeterminate	%	0	0	23	0			
Negative	%	100	0	0	100			
Positive	%	0	100	77	0			
COVID Specific IgG titer						<.001***	<.001***	1.000
n/a	%	100	0	23	100			
1:800	%	0	0	6	0			
1:1,600	%	0	6	14	0			
1:3,200	%	0	0	20	0			
1:6,400	%	0	9	6	0			
>1:12,800	%	0	84	31	0			

[a]Missing data imputed for 1 patient.
[b]Missing data imputed for 4 patients.
*$p < 0.050$.
***$p < 0.0167$ (Below Bonferroni correction).

the lack of statistical elevations in ferritin and CRP levels in our infants.

IL-6 is an important cytokine that participates in placental health (29). A recent study of mothers with COVID-19 infection who underwent chorionic villous and chorioamniotic membrane biopsy, reviewed innate cytokine production by the fetus (9). Expression of interferon type 1 and IL-6 genes were noted to be low in delivered placental tissue even if the mother was infected with COVID-19 (9). In fact, altered innate cytokine gene expression was still evident in placental biopsies of mothers who were completely recovered from COVID-19 (9). CRP and ferritin were normal in all groups we tested, and the lack of elevation of these in our study suggests it was unlikely that elevated IL-6 maternal cross-placental transfer or fetal production of IL-6 in

our dyads was demonstrated (9) as we did not demonstrate an increase in fetal acute phase reactants in our study.

While calcium and inactive Vitamin D metabolites can cross the placenta, it is thought that Vitamin D is largely of placental origin, being synthesized by the placenta and fetal kidney tissues (30). Additionally, Vitamin D's effects on inflammation are to inhibit Th1 proliferation and induce Th2 proliferation, thus assisting in downregulating inflammation which may harm the fetus (31). Maternal deficiencies in pregnancy can contribute to poor placental outcomes, such as issues with implantation in early pregnancy or pre-eclampsia in late pregnancy (19). It is known that healthy maternal populations and non-pregnant females of childbearing age in northern latitudes are typically Vitamin D insufficient (32). In our study, there was little variability observed in our groups, with optimal levels of Vitamin D observed across all 4 groups. This suggests that elevated placental Vitamin D is not required for anti-inflammatory responses to vaccination or maternal COVID-19 disease.

In measuring cortisol, however, we noticed a comparable difference between our infants from vaccinated mothers (Vaccinated), as well as our infants born to mothers who had COVID-19 several weeks prior to delivery, mounting a measurable IgG response (Unvaccinated/SARS-CoV-2(+)/IgG(+)). In these two groups, cortisol was 100% and 60% higher as compared to our Control group respectively. There is evidence that maternal cortisol can cross the placenta and is also thought to be a marker of neonatal stress suggesting that this hormone is critical to maintaining maternal/fetal homeostasis (23). Our elevated cortisol infants had unremarkable newborn nursery courses. The only commonality was their assigned groups of Vaccinated or SARS-CoV2(+)/IgG(+). A smaller percentage of these neonates appeared to have fewer NICU admissions (34% in vaccinated and 14% in SARS-CoV2(+)/IgG(+) as compared to 40% of controls) thus it could be postulated that this stress response potentially contributed to a smoother birth transition excluding the need for a NICU admission. Both groups conceivably experienced inflammation during either vaccination or disease. Demonstrated elevations in cortisol in our study suggest that either mother, fetus, or both inherently tried to achieve homeostasis *via* cortisol to control the damaging effects of inflammation on the fetus. Cortisol is known to decrease NF-κB production of innate cytokines such as IL-1 and IL-6 (33). Our novel study may, in fact, suggest a biologically plausible reason for the lack of innate cytokine production found in biopsied placentas of COVID-19 infected mothers (9).

Our prospective, proof of concept, single-centered study, was small. A larger sample size in the future would enable more robust findings; however, to account for our sample size, we utilized conservative effect estimates calculated using Bonferroni corrections to limit the risk of type I statistical errors. Future studies would be illuminating to include maternal blood sampling to verify cytokine and complement levels and maternal cortisol findings to corroborate our study. Due to the rapid onset of the COVID-19 pandemic, multiple health systems and electronic medical records were not prepared to document patient encounters during the pandemic. As such, our documentation relied on an EMR review of PCP records for testing results or vaccination cards provided by mothers who brought this data to the delivery room. Key strengths of our study were the completeness of our dataset and requiring limited utilization of imputations for missing data. Our novel study demonstrated a statistically significant increase in cortisol which is needed to control neonatal inflammation, but acute phase reactant elevations were not noted. As such, our study may not have accounted for early timing to detect very early innate immune responses and subsequent production of ferritin or CRP yet yielded the downstream anti-inflammatory result of elevated neonatal cortisol levels. In addition, future studies of mothers with long COVID-19 might determine if the development of heightened cortisol levels is due to smoldering inflammation.

We hypothesized in this novel study that either COVID-19 disease or the mRNA vaccine might have inflammatory effects on fetal indices of inflammation such as CBC, ferritin, and CRP. While the CBC showed no variation, but for MPV, the clinical implications of MPV variation at birth are not known. In this novel study attempting to define inflammatory and anti-inflammatory changes notable to a fetus after maternal COVID disease or vaccination, we found that cortisol levels were elevated in these dyads. This finding is important because cortisol may be an important anti-inflammatory response to the innate immune system activation associated with COVID-19 disease or the mRNA vaccine. In addition, a cortisol elevation may provide a hypothesis for previous research determining the lack of fetal gene expression of innate cytokines during maternal COVID-19 infection. Future studies of both maternal and fetal cytokine and complement responses to disease and mRNA vaccination will help elucidate how mother/infant dyads achieve homeostasis in the face of inflammatory challenges.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Marshall University Internal Review Board #1 (Medical) IRB# 1726140. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

BG, EM, AR, and DM developed the study concept. BG, MBH, EM and DP designed the study. EM, MBH, GM, BG and AR performed the literature review. BG, JH, JN, KA, HW, EM, MN,

DP, AR, GM, DM, and JC acquired the data. MN performed the statistical analysis. EM, MN, MBH, and DP drafted the manuscript. EM, MBH, JN, MN, CM, DP, and BG provided critical revisions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Acute hepatitis in neonates with COVID-19 during the Omicron SARS-CoV-2 variant wave: a report of four cases

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Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first emerging in December 2019 and continuously evolving, poses a considerable challenge worldwide. It was reported in the literature that neonates had mild upper respiratory symptoms and a better outcome after Omicron SARS-CoV-2 variant infection, but there was insufficient data about complications and prognosis.
Case Presentation: In this paper, we present the clinical and laboratory characteristics of four COVID-19 neonate patients with acute hepatitis during the Omicron SARS-CoV-2 variant wave. All patients had a clear history of Omicron exposure and were infected via contact with confirmed caregivers. Low to moderate fever and respiratory symptoms were the primary clinical manifestations, and all patients had a normal liver function at the initial stage of the course. Then, the fever lasted 2 to 4 days, and it was noted that hepatic dysfunction might have occurred 5 to 8 days after the first onset of fever, mainly characterized by moderate ALT and AST elevation (>3 to 10-fold of upper limit). There were no abnormalities in bilirubin levels, blood ammonia, protein synthesis, lipid metabolism, and coagulation. All the patients received hepatoprotective therapy, and transaminase levels gradually decreased to the normal range after 2 to 3 weeks without other complications.
Conclusions: This is the first case series about moderate to severe hepatitis in COVID-19 neonatal patients via horizontal transmission. Besides fever and respiratory symptoms, the clinical doctor should pay much attention to evaluating the risk of liver function injury after SARS-CoV-2 variants infection, which is usually asymptomatic and has a delayed onset.

KEYWORDS
neonate, SARS-CoV-2, Omicron variant, COVID-19, acute hepatitis, liver injury, transaminase

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first emerging in December 2019 and continuously evolving to different variants through gene mutations, brought tremendous challenges and burdens to global public health (1–3). Since a new Omicron variant was discovered in November of 2021 in South Africa, it quickly spread worldwide and has replaced the Delta variant as the dominant pandemic strain (4, 5). The Omicron variant has identified a much greater number of mutations than any

previous strains. The mutations, mainly on the spike protein of the virus, significantly increase binding affinity to human ACE2 receptors, contributing to immune evasion property and transmission fitness (6, 7). Compared with previous strains, the Omicron variant is more transmissible and easy to infect younger individuals (8). The literature on neonates with Omicron variant infection is limited; most of them are perinatal cases (9, 10). Xu et al. reported mild upper respiratory symptoms and a better outcome for neonates during the Omicron variant wave in Shanghai (11). However, there is insufficient data on the complication and prognosis for neonates with Omicron variant infection. As far as we know, there have been few reports about liver injury accompanied by Omicron variant infection in neonates, which is a rare symptom. Therefore, we present the clinical characteristics and outcomes of four Omicron-infected neonate patients with acute hepatitis in this study.

Case presentation

Case 1

A 27-day-old boy presented to the emergency room with a 7-hour history of fever. After giving superficial skin cooling at home, the baby remained febrile. The peak temperature was 38.5°C. The baby had a poor appetite and symptoms of sneezing and a stuffy nose without vomiting and coughing. He was a term baby without extraordinary perinatal history. His parents had a history of sore throat and cough for several days during the Omicron epidemic, but they didn't test for SARS-CoV-2. After admission to our NICU, he was febrile at 38.3°C with a respiratory rate of 52 breaths/min and oxygen saturation of 95%–99% while breathing ambient air. His examination was remarkable for congested nares, clear rhinorrhea, and mild subcostal retractions. There were coarse breath sounds in all lung fields. No murmur of the heart could be heard. The liver was palpated at 1 cm–2 cm under the costal margin (consistent with age), and the spleen was not palpated. Laboratory data revealed that the total WBC count and the proportions of the major leukocyte subsets in peripheral blood were normal. Blood gas, C reactive protein (CRP), and transaminase levels were in the normal range. RNA test for SARS-CoV-2 from a throat swab was positive. Then, the baby was given physical cooling and nasal secretion removal to keep the airway clear (see **Table 1**).

The baby presented febrile once daily in the following four days, and the peak temperature decreased from 38.4 to 38°C. Meanwhile, he developed a cough and sputum, along with a dropping of SpO2 to 80% when feeding. His lung demonstrated scattered crackles (see **Figure 1**). Because of continuous fever and pneumonia, more investigations were performed. The total WBC count and the proportions of the major leukocyte subsets were still in the normal range. CRP was 4.3 mg/L (0–10 mg/L). Anemia was noticed: RBC was 2.73 × 1,012/L, hemoglobin was 91.0 g/L, and hematocrit was 27.4%. Alanine transaminase (ALT) was 88 U/L(≤41 U/L), aspartate transaminase (AST) was 180 IU/L(≤40 U/L), and glutamyltranspeptidase (γ-GT) was 109 U/L(6–42 U/L). Further, pathogens tests identified that parainfluenza virus RNA was positive, but there was no evidence of infection for other pathogens such as RSV, EBV, TORCH, ECHO virus, Coxsackie virus (CA16/CVB), influenza A/B/H1N1/H3N2, adenovirus, mycoplasma, chlamydia, HIV, Human metapneumovirus, rhinovirus, and hepatitis B/C virus. Ultrasonography for the heart and abdomen was normal. Therefore, the baby was given the nebulization treatment of budesonide and ipratropium bromide solution and given Glutathione for hepatoprotection. In addition, he inhaled oxygen intermittently to avoid hypoxia when feeding.

On the 7th day after admission, the patient was no longer febrile but was still coughing and had nasal congestion. On the 10th day, respiratory symptoms improved greatly, and we re-tested the liver function after 5 days of hepatoprotective treatment. The transaminase level elevated markedly. ALT was up to 645 U/L (≤41 U/L), AST increased to 480 IU/L(≤40 U/L), and γ-GT was 491 U/L(6–42 U/L). However, bilirubin, blood ammonia, blood glucose, lipids, lactate, coagulation function, and albumin levels were within the normal range. The patient's perinatal medical history and family history were tracked carefully, and the possibility of inherited metabolic liver disease was ruled out. Furthermore, the patient's history of drug exposure before/after admission was also reviewed, and there was no evidence of drug-induced liver injury. So, virus infection may contribute to liver injury and the elevation of transaminase levels. When the immune system clears the virus, the injury should be alleviated. Thus, we only administered glycyrrhizin and bicyclol to promote recovery.

On the 14th day, the baby looked well with the normal physical examination. Laboratory tests demonstrated that ALT decreased to 125 U/L(≤41 U/L), AST was 44 IU/L(≤40 U/L), and γ-GT was 283 U/L(6–42 U/L). He continued to take glycyrrhizin and bicyclol after being discharged home. The liver transaminase level returned to normal on 8 and 15 days after discharge (see **Table 2** and **Figure 2**).

Case 2

A 7-day-old girl was admitted to our NICU because of a 30-hour intermittent fever with a peak temperature of 38.5°C. Her parents noted that she had a stuffy nose with clear rhinorrhea and choked when feeding over the past two days. She coughed occasionally but had sputum in her throat. Her appetite was unchanged without increasing work of breathing, vomiting, and diarrhea. Her caregivers had confirmed infection of SARS-CoV-2 several days ago. Her mother was healthy during pregnancy but detected fetal hydronephrosis with the right duplex kidney in the third trimester. The baby was born through an uneventful C-section delivery at a gestational age of $40w^{+6}$. The baby looked well after birth, and there was no evidence of early-onset sepsis. On physical examination, she had a temperature of 38.6°C and mild tachypnea of a respiratory rate of 50 breaths/min without retraction. Her lungs demonstrated coarse breath sounds without crackles and wheezes. The lab

TABLE 1 Summary of clinical presentation and outcome of COVID-19 neonate cases with acute hepatitis.

No.	Age of onset (d)	GA (g)	BW (g)	Wt (g)	Epidemiological exposure history			Comorbidity	Symptom	Chest radiology	Ultrasound	Peak Temp (°C)	Fever duration (days)	Special abnormal finding	Pathogens		Treatment	Recovery/Outcome	
					Epidemic	Contact history	Mother's vaccination								SARS-CoV-2	Others*		Respiratory symptoms (d)	Liver function**
1	27	38 weeks	3,400	4,640	Omicron variant	The parent had a history of sore throat and cough for several days without COVID-19 test.	no	No	Fever; Anorexia; stuffy nose; sneeze; cough and sputum; SpO2 dropped to 80% when feeding	x-rays: increased and blurred bilateral lung markings	Cardiac/ abdominal US (−)	38.5	7 days	Found elevated liver enzymes after 5 days of fever;	PCR for RNA (+)	Parainfluenza virus (oropharyngeal swab)	Superficial skin cooling; oxygen inhalation when feeding; nebulization; hepatoprotective drugs	10 days	21 days
2	7	$40w^{+6}$	4,020	3,600	Omicron variant	Mother confirmed infection	Two does	Congenital Hydronephrosis (bilateral, mild); right renal calculus (3.1 × 2.7 mm)	Fever; choking on milk, spitting; stuffy nose; cough occasionally	x-rays: increased and blurred bilateral lung markings	Cardiac US: PFO 2.6 mm (left-to-right shunt); EF: 68%; kidney US: mild bilateral hydronephrosis and calculus in the right kidney (3.1 mm × 2.7 mm); liver/ gallbladder/ spleen US: (−)	38.7	3 days	Found elevated liver enzymes after 7 days of fever	RNA and antigen: (+)	None	Superficial skin cooling; piperacillin/ tazobactam; hepatoprotective drugs	9 days	18 days
3	15	40 w	3,350	3,530	Omicron variant	Caregivers confirmed infection	no	No	Fever; stuffy nose and runny nose; mild cough; coarse and wet rales	x-rays: increased and blurred bilateral lung markings, and patchy shadows on the right upper lung field.	Cardiac/ abdominal US (−)	38.3	3 days	Found elevated liver enzymes after 8 days of fever	(+)	None	Superficial skin cooling; piperacillin/ tazobactam; hepatoprotective drugs	11 days	14 days
4	24	$36w^{+4}$	3,050	4,680	Omicron variant	Mother confirmed infection	no	No	Fever, anorexia, cough and sputum; watery diarrhea; cough occasionally; skin markings on lower extremity	x-rays: increased and blurred bilateral lung markings	Cardiac/ abdominal US (−)	38	3 days	Found elevated liver enzymes after 7 days of fever	(+)	None	Superficial skin cooling; empirical antibiotics for 36 h; hepatoprotective drugs;	10 days	10 days

*Others: RSV, EBV, TORCH, ECHO virus, Coxsackie virus(CA16/CVB), influenza A/B/H1N1/H3N2, adenovirus, mycoplasma, chlamydia, HIV, Human metapneumovirus, rhinovirus, and hepatitis B/C virus.
**Liver function: the duration of ALT decreasing to the normal range.

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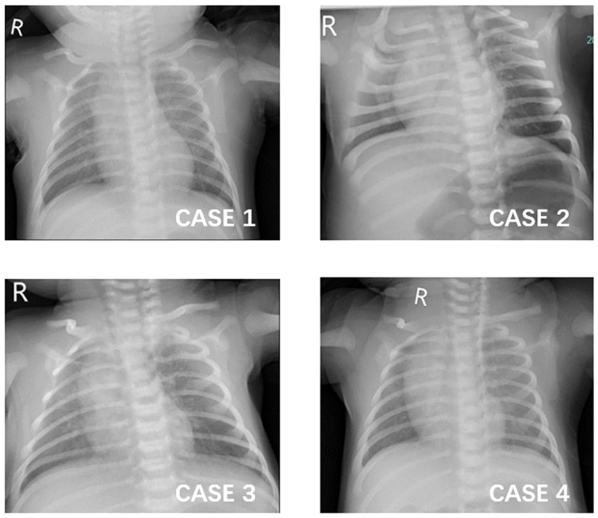

FIGURE 1
Chest x-ray images of the four patients. (1) CASE 1: increased and blurred bilateral lung markings. (2) CASE 2: increased and blurred bilateral lung markings. (3) CASE 3: increased and blurred bilateral lung markings and patchy shadows on the right upper lung field. (4) CASE 4: increased and blurred bilateral lung markings.

investigations showed that CRP was increased to 19.8 mg/L(0–10 mg/L) (see Table 1).

WBC, blood gas analysis, transaminase level, and bilirubin levels were all in the normal range. The blood culture for bacteria was negative. Chest x-rays suggested increased and blurred bilateral lung markings in both lung fields (see Figure 1). Cardiac ultrasound demonstrated a left-to-right shunt of 2.6 mm through a patent foramen ovale (PFO). Abdominal ultrasound showed mild bilateral hydronephrosis and calculus in the right kidney (3.1 mm × 2.7 mm), and there were no abnormalities in the liver, gallbladder, and spleen structures. PCR and quick antigen tests for SARS-CoV-2 from the throat swab were positive. There was no evidence of infection from other viruses [RSV, EBV, TORCH, ECHO virus, Coxsackie virus (CA16/CVB), influenza A/B, adenovirus, mycoplasma, chlamydia, HIV, Human metapneumovirus, rhinovirus, and hepatitis B/C virus]. Normal saline helped to clean the airway, and nasal drops were used to relieve nasal congestion. Moreover, superficial skin cooling was given when the baby was febrile, and piperacillin/tazobactam was administered for pneumonia.

The baby's body temperature declined to normal on the 2nd day after admission. The respiratory symptom alleviated over the following days. On the 6th day, the laboratory tests showed that the transaminase level increased significantly without abnormality of bilirubin and albumin (see Table 2 and Figure 2). Then, the hepatoprotective treatment of glycyrrhizin and bicyclol was administered.

ALT decreased by half on the 11th day. Given that the baby had recovered from fever and respiratory symptoms, she was discharged home with oral drugs of glycyrrhizin and bicyclol and was continued to be followed up in the outpatient department. Two weeks later, lab tests suggested that ALT and AST decreased to the normal range.

Case 3

A 15-day-old girl was brought to the emergency center with a 2-day recurrent fever after contracting confirmed cases of COVID-19. The peak temperature was 38.1°C. Besides fever, she had a stuffy nose and a mild cough. She did not develop diarrhea and vomiting during the course. She had no complicated perinatal history. Her examination was febrile at 38.1°C with a respiratory rate of 48 breaths/min and oxygen saturation of 98%–100%. She had normal respiratory effort, and coarse breath sounds could be heard in all lung fields. Lab data of the WBC, CRP, blood gas, transaminase levels, and bilirubin levels were all in the normal range. The PCR test was positive for SARS-CoV-2 without other positive findings of other pathogens [RSV, EBV, TORCH, ECHO virus, Coxsackie virus (CA16/CVB), influenza A/B, adenovirus, mycoplasma, chlamydia, HIV, Human metapneumovirus, rhinovirus, and hepatitis B/C virus]. After admission, the baby was given the nebulization treatment of budesonide and ipratropium bromide, using normal saline and nasal drops to relieve nasal congestion and keep the nasal cavity clean (see Table 1).

The baby returned to normal temperature and developed frequent coughs over the days. Her lung examination demonstrated scattered crackles on the back side, and then, phlegm and wheezing sounds could be heard in the following days. Chest x-rays showed that bilateral lung markings increased and blurred, with patchy shadows on the right upper lung field (see Figure 1). The piperacillin/tazobactam for pneumonia was administered on the fourth day after admission. Since then, her symptoms and signs of respiratory improved gradually.

The baby got better on the 6th day after admission with wild nasal congestion. Laboratory tests showed that ALT and AST increased significantly (see Table 2 and Figure 2). She was also administered hepatoprotective treatment of glycyrrhizin and bicyclol. After a 2-week treatment, the liver function recovered totally.

Case 4

A 24-day-old boy was admitted to the NICU for an 8-hour history of fever with a peak temperature of 38°C. The parents complained that the baby had a mild cough with sputum, and they noticed he seemed to have facial and lip cyanosis when feeding. The baby was lethargic and had a poor appetite, accompanied by watery diarrhea without emesis. He was born at a gestational age of $36w^{+4}$ via cesarean delivery. He had no remarkable perinatal history. His mother confirmed COVID-19 with fever and cough before he had symptoms. On physical examination, his temperature was 38°C with a respiratory rate of 46 breaths/min; blood pressure was in the normal range, and his SpO2 was 97% while feeding and breathing ambient air. Coarse breath without crackling sounds in all lung fields could be heard. No heart murmur was detected. Prominent reticulated mottling of the skin could be seen on the lower

TABLE 2 Laboratory data on presentation of COVID-19 neonate cases with acute hepatitis.

No.		Duration after fever	ALT (≤41 U/L)	AST (≤40 U/L)	r-GT (6–42 U/L)	DB (≤8.0)	Ammonia (16–60)	WBC 5–20 × 10^9/L	*N*% (45%–70%)	*L*% (30%–50%)	*M*% (4.0%–11.0%)	CRP (0–10 mg/L)	IL-6 <7 pg/ml	PCT (<0.5 ng/ml)	PT (11.5–14.0)	APTT (36–49)	Fib (1.7–4.1)	D-D (<0.5)	CnTI (<88 pg/ml)	Metabolic screen*
1	admission	7 h after fever	33	40	112	6.4		5.07	36.1	29.2	29.6	1.1								
	D5	5 days after fever	88	180	109	2.5		4.72	33.7	57	8.9	4.3								
	D10	10 days after fever	645	480	491	3.2		12.37	31.8	58.9	7.8	2.2							28.8	
	D11	11 days after fever					48								12.3	36.8	2.92	0.91		(−)
	D14	14 days after fever	125	44	283	2.8		11.45	23	66.9	7.9	0.2								
	D18/discharge																			
	8 days after discharge	follow up-1	32	73	163	2.1		9.64	28.4	54.1	10.3									
	15 days after discharge	follow up-2	38	81	119	2.2														
2	admission	30 h after fever	9	32	155	12.9		10.02	61.6	25.9	11.6	19.8							55.5	
	D2	3 days after fever						8.37	39.9	43.8	13.6	7.5								
	D6	7 days after fever	280	414	289	5		6.42	32.2	53.1	12	12.4		<0.1						
	D8	8 days after fever										1.87								
	D11	11 days after fever	197	242	596	3.6														
	D12/discharge																			
	13 days after discharge	follow up-1	10 (8–71)	26 (21–80)	325 (9–150)	2.1 (0–4)														
3	admission	2 days after fever	15	34	144	6.4		17.14	61.6	25.9	11.6	1.6								
	D2	4 days after fever	13	34	107	4.8		6.7	25.1	60.9	12.4	0.3								
	D6	8 days after fever	268	286	182	5.5		12.08	19.5	61.3	16.4	1.4								
	D10	12 days after fever	45	29	117	3.0						<0.5								
	D12/discharge																			
	9 days after discharge	follow up-1	11	21	54	4.5														
4	admission	1 days after fever	20	29	129	9.1		4.61	30.4	46.4	18.2	<0.5	6.02	0.13						
	D6	7 days after fever	151	234	151	<1.6		9.96	9.7	83.2	5.8	<0.5			10.4	37.4	2.03	2.36		
	D11	12 days after fever	97	40	212	4.5						<0.5								
	D12/discharge																			
	4 days after discharge	follow up-1	26	32	148	3.3		11.58	28.2	64.2	6.2									

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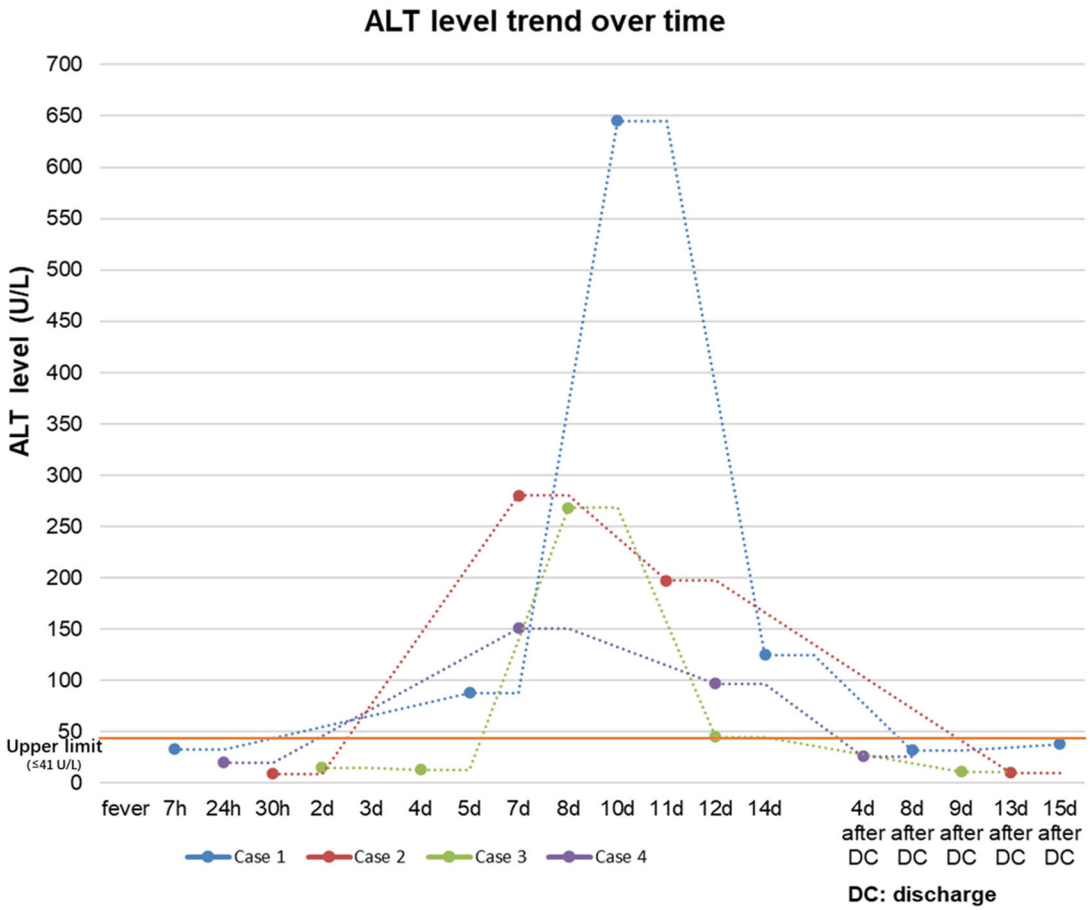

FIGURE 2
ALT level trend over time of the four patients. All patients had normal liver function at the initial stage of the course. ALT elevation (>41 U/L) occurred 5 to 8 days after the first onset of fever, then reached 3 to 10 folds of the upper range. All the patients received hepatoprotective therapy, and transaminase levels gradually decreased to the normal range after 2 to 3 weeks.

extremities, especially when he was febrile. Capillary refill time in the lower extremity was 2 s. The liver was palpated at 1 cm under the costal margin, and the spleen was not palpated. Laboratory data revealed that WBC, subsets proportion, CRP, procalcitonin (PCT), blood gas, electrolytes, transaminase, and bilirubin levels were all in the normal range. Blood culture was negative. No other apparent abnormalities were reported on the routine stool test. PCR test for the SARS-CoV-2 virus was positive. The common respiratory pathogens such as influenza A/B, RSV, parainfluenza, adenovirus, mycoplasma, and chlamydia were negative. Chest x-rays showed that bilateral lung markings increased and blurred (see **Figure 1**). The cardiac ultrasound was normal. The CRP tests were repeated, and sepsis was ruled out in the next few days. So, the baby was administered piperacillin/tazobactam for 36 h and nebulization treatment was given (see **Table 1**).

The fever lasted for 2 days, and the peak temperature was 38.6° C. The baby recovered with occasional cough and mild nasal congestion on the 5th day after admission. On the 6th day, the ALT and AST were significantly increased (see **Table 2** and **Figure 2**). There was no evidence of infection for other pathogens related to liver injuries such as EBV, TORCH, ECHO virus, Coxsackie virus (CA16/CVB), and hepatitis B/C virus. He was also administered hepatoprotective treatment of glycyrrhizin and bicyclol.

The baby received hepatoprotective treatment for 5 days. On the 11th day after admission, repeated lab tests demonstrated that ALT and AST decreased to 97 U/L and 40 IU/L, respectively. Then he was discharged with hepatoprotective drugs. 4 days after discharge, the liver function went back to the normal range.

Discussion

We presented four COVID-19 cases with hepatic injury for newborn infants in the SARS-CoV-2 variants Omicron epidemic. All patients had a normal liver function at the initial stage of the course. It was noted that hepatic dysfunction might have occurred 5 to 8 days after the first onset of fever, mainly characterized by moderate to severe transaminase elevation and without abnormalities in bilirubin level, blood ammonia, protein synthesis, lipid metabolism, and coagulation. All the patients

received hepatoprotective therapy, and transaminase levels gradually decreased to the normal range after 1 to 2 weeks.

Liver involvement in adult patients with COVID-19 has been reported previously (12–14). As for Children suffering from COVID-19, they usually present mild or asymptomatic diseases. The liver involvement, characterized by the elevation of transaminases without hepatic synthetic dysfunction, could be seen in critically ill patients with multisystem inflammatory syndromes (MIS) secondary to SARS-CoV-2 infection (15, 16). Moreover, several cases in the literature reported that some children with an asymptomatic or mild presentation of COVID-19 disease developed long COVID-19 liver manifestations, including acute liver failure or acute hepatitis with cholestasis. The outcome varies widely from life-threatening and a need for liver transplant to total recovery after steroid treatment (17–20). Reports in the literature on liver involvement in neonates with SARS-CoV-2 infection were sparse. Stolfi et al. reported that a newborn patient infected with SARS-CoV-2 vertically without respiratory manifestations had an elevation of serum liver enzymes after birth (the peak of ALT and AST were 155 and 143 U/L, respectively) and gradually recovered on the day of life DOL10 (9). Another case from Sisman et al. presented a preterm infant with SARS-CoV-2 infection via intrauterine transmission, who developed a fever and mild respiratory disease on the second day of life, only had a slightly increased AST (64 U/L, normal range 10–35) and normal level of ALT (10). Compared with these two patients, babies in our case series were infected by contact with caregivers, the onset was late, and the liver injury was much more severe. Therefore, this is the first case series about moderate (ALT or AST is within 3 to 10 folds normal upper limit) to severe (ALT or AST >500 U/L or >10-fold normal upper limit) hepatitis in COVID-19 neonatal patients via horizontal transmission.

The potential mechanism of SARS-CoV-2 virus infection-associated liver injury could be attributed to hepatic tropism and direct cytopathic effects (21, 22). Hepatic biopsy pathology from a COVID-19 patient revealed that the SARS-CoV-2 virus could be seen in vessel lumens, endothelial cells of the portal vein, and the cytoplasm of hepatocytes, which leads to hepatocytic apoptosis (23, 24). Cytokine storm and MIS secondary to SARS-CoV-2 infection could also result in immune-mediated hepatocellular damage, albumin synthesis suppression, and cholestasis (21, 25, 26). Furthermore, hypoxia from acute respiratory and cardiac failure could also contribute to liver injury in critically ill patients (12, 13). Patients in this group are expected to be accompanied by hypoxic-ischemic myocardial injury. In addition, various drugs in clinical practice also contribute to liver injuries such as antiviral drugs, long-term antibiotics, corticosteroids, and antipyretic drugs (acetaminophen) (13, 22).

It was interesting that one patient in our group, suffering from longer fever duration and more severe liver injury, was co-infected with the SARS-CoV-2 virus and parainfluenza virus (PIV). To the best of our knowledge, PIV mainly causes respiratory tract illnesses such as bronchiolitis, pneumonia, and croup, and n on-respiratory manifestations are rare without reports of related liver involvement (27–30). Meanwhile, we ruled out the infection of other common viruses which could induce liver injuries such as RSV, EBV, TORCH, ECHO virus, Coxsackie virus (CA16/CVB), influenza A/B/H1N1/H3N2, adenovirus, mycoplasma, chlamydia, HIV, Human metapneumovirus, rhinovirus, and hepatitis A/B/C virus. Similar reports about severe acute hepatitis (SAH) of unknown etiology across multiple countries from January 2022 to June 2022 demonstrated that 91 of the 126 children (72%) suffered from the adenovirus infection; however, adenovirus alone is rarely associated with acute hepatic failure in healthy children (31). Further, Akash et al. reported that six of the eight children who developed liver failure and received liver transplants were all infected with the novel coronavirus (SARS-CoV-2 antibody positive); it was worth noting that adenovirus was detected in their whole blood samples but was undetected in the liver biopsies (32). Thus, it may speculate that virus co-infection may contribute to the severity of COVID-19 disease and aggravate related liver injury.

In addition, we also try to exclude other causes leading to liver injury. Firstly, all patients with mild or moderate fever were not administered antipyretic drugs for fever and other liver-injured medicines, so we could exclude the possibility of antipyretic drug-induced liver injury, which may be the confounding factor of liver involvement in some critically ill cases. The patient in Case 1 didn't receive antibiotics treatment, but patients in the other three cases were administered piperacillin/tazobactam in the short course. It was reported that piperacillin/tazobactam could lead to hepatotoxicity and drug-induced liver injury (DILI), which was the most common causative antibiotic of DILI in adults (33). However, the use of piperacillin/tazobactam in neonatal and pediatric patients is safe and effective as an empiric treatment for serious infections. Severe adverse events related to piperacillin/tazobactam use are hemolytic anemia, pustulous skin eruptions, drug hypersensitivity syndrome, and neutropenia and are time and dose-dependent (34, 35). Further study is needed to explore the incidence and severity of piperacillin/tazobactam-induced liver injury in a large population of neonatal and pediatric patients in a real-world setting. Secondly, the parents denied the related perinatal history and the mother's preview medical history of autoimmune disease. The babies did not present the abnormal direct bilirubin level, and all recovered without corticosteroid treatment in follow-up, so there was little evidence to support the diagnosis of autoimmune liver dysfunction. Thirdly, all the patients grew well without abnormal results of blood PH/base excess, lactate, blood ammonia, and pyruvic acid. Thus, metabolic liver disease could be ruled out. Lastly, none of the patients presented symptoms of MIS or hypoxia from acute respiratory distress, and two of them had normal levels of IL-6 and CnTI. Therefore, it can be concluded that the leading cause of acute hepatitis in these patients was the Omicron SARS-CoV-2 variant infection.

In our case series, we presented four COVID-19 neonate patients with liver involvement, describing the trend of transaminase over time and the short outcome. Based on these limited cases, it is hard to deeply explore and analyze population characteristics and risk factors for liver injury. We also lack reliable biomarkers to detect liver injury early in neonates with SARS-CoV-2 infection. Additionally, long-term follow-up is needed to ensure full recovery

for the patients. Moreover, all the patients received hepatoprotective treatment, including glycyrrhizin, glutathione, or bicyclol. Glycyrrhizin (Magnesium isoglycyrrhizinate) is a hepatocyte protectant with anti-inflammatory effects and protection of the liver cell membrane. Glutathione is a strong antioxidant that could improve membrane stability to protect the liver cell membrane, promote detoxification, and repair enzyme activity. Bicyclol could protect the liver cell membrane by clearing free radicals, protect liver cell nuclear DNA from damage, and reduce the occurrence of apoptosis. These drugs, which are also used in the treatment of chronic viral hepatitis in adults, may help decrease the ALT and recover liver function.

This study is not a strict RCT trial or a well-designed cohort study. There are potential biases and cofounders which may affect the conclusion. In this case-serial report, no control group could balance some related factors, which is also our limitation in this study.

Conclusions

Newborns are a high-risk group for COVID-19 in the condition of postnatal infection during the Omicron variants epidemic. Besides fever and respiratory symptoms, the clinical doctor should pay much attention to evaluating the risk of liver function injury after SARS-CoV-2 variants infection, which is usually asymptomatic and has a delayed onset. If the patient was co-infected with other pathogens, the symptoms and signs might be severe and long-lasting. It takes time for liver function recovery, so the patient should be followed up closely after discharge. Further research is needed to provide more evidence in the future.

Data availability statement

All relevant data is contained within the article: the original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for publication of clinical details and clinical images was obtained from the patient's legal guardian for publication.

Author contributions

JW and ZR proposed and designed the study. WH, KW, and RY helped design the study and collected data. JW analyzed the data and wrote the original draft. LC and ZR critically reviewed and revised the draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuroimaging assessment of pediatric cerebral changes associated with SARS-CoV-2 infection during pregnancy

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Background: SARS-CoV-2 infection and perinatal neurologic outcomes are still not fully understood. However, there is recent evidence of white matter disease and impaired neurodevelopment in newborns following maternal SARS-CoV-2 infection. These appear to occur as a consequence of both direct viral effects and a systemic inflammatory response, with glial cell/myelin involvement and regional hypoxia/microvascular dysfunction. We sought to characterize the consequences of maternal and fetal inflammatory states in the central nervous system of newborns following maternal SARS-CoV-2 infection.

Methods: We conducted a longitudinal prospective cohort study from June 2020 to December 2021, with follow-up of newborns born to mothers exposed or not exposed to SARS-CoV-2 infection during pregnancy. Brain analysis included data from cranial ultrasound scans (CUS) with grayscale, Doppler studies (color and spectral), and ultrasound-based brain elastography (shear-wave mode) in specific regions of interest (ROIs): deep white matter, superficial white matter, corpus callosum, basal ganglia, and cortical gray matter. Brain elastography was used to estimate brain parenchymal stiffness, which is an indirect quantifier of cerebral myelin tissue content.

Results: A total of 219 single-pregnancy children were enrolled, including 201 born to mothers exposed to SARS-CoV-2 infection and 18 from unexposed controls. A neuroimaging evaluation was performed at 6 months of adjusted chronological age and revealed 18 grayscale and 21 Doppler abnormalities. Predominant findings were hyperechogenicity of deep brain white matter and basal ganglia (caudate nuclei/thalamus) and a reduction in the resistance and pulsatility indices of intracranial arterial flow. The anterior brain circulation (middle cerebral and pericallosal arteries) displayed a wider range of flow variation than the posterior circulation (basilar artery). Shear-wave US elastography analysis showed a reduction in stiffness values in the SARS-CoV-2

exposed group in all analyzed regions of interest, especially in the deep white matter elasticity coefficients (3.98 ± 0.62) compared to the control group (7.76 ± 0.77); p-value < 0.001.

Conclusion: This study further characterizes pediatric structural encephalic changes associated with SARS-CoV-2 infection during pregnancy. The maternal infection has been shown to be related to cerebral deep white matter predominant involvement, with regional hyperechogenicity and reduction of elasticity coefficients, suggesting zonal impairment of myelin content. Morphologic findings may be subtle, and functional studies such as Doppler and elastography may be valuable tools to more accurately identify infants at risk of neurologic damage.

KEYWORDS

COVID, SARS-CoV-2, pregnancy, neonatology, ultrasound, elastography, neuroimaging

1. Introduction

Maternal infection with SARS-CoV-2 during pregnancy may expose the fetus to both direct and indirect systemic effects triggered by the virus (1). The consequences of the maternal and fetal inflammatory response with the production of potentially cytotoxic cytokines, in addition to the effect of the use of antiviral medications, have not been adequately studied to date (1, 2).

There is evidence that vascular complications may result from the potential hyperactivation of inflammatory factors and coagulation system dysfunction, particularly D-dimer and platelet abnormalities, increasing the risk of cerebrovascular disease, myelination defects, and hypoxic-ischemic encephalopathy following exposure to SARS-CoV-2 (3, 4). The potential consequences of changes in intracranial blood flow dynamics and cerebral hypoxia, mediated by systemic inflammatory response syndrome (SIRS), are still poorly elucidated in the pediatric age group (5). This study aimed to investigate the effects of maternal SARS-CoV-2 infection on the brains of infants exposed to SARS-CoV-2 infection during pregnancy, focusing on brain morphological changes, intracranial blood flow dynamics, and parenchymal composition/stiffness analysis. Additionally, we sought to assess the clinical and neurodevelopmental outcomes of newborns following maternal SARS-CoV-2 infection.

2. Methods

2.1. Study design and population

A prospective, comparative, and analytical cohort study was conducted with the follow-up of newborns born to mothers exposed or not exposed to SARS-CoV-2 infection during pregnancy. The study population consisted of 219 children, of whom 201 were in the group of newborns born to women infected by SARS-CoV-2 at different stages of pregnancy. The control group consisted of 18 newborns born to women who remained serologically negative for SARS-CoV-2 until the end of the neonatal period. Study recruitment was from May 2020 to June 2022, during the COVID-19 pandemic, with planned clinical, neurological, and psychomotor follow-up until December 2022. Clinical follow-up was performed monthly until 6 months of age and then quarterly until 24 months of age. A global pediatric assessment and a neuro-psychomotor development diagnostic scale (Bayley III scale) were administered quarterly. Neuro-ultrasonography, color/spectral Doppler, and shear-wave elastography studies were performed at 6 months of adjusted chronological age, and follow-up evaluation was completed 4 weeks later for the abnormal cases. Detailed maternal clinical characteristics were also prospectively collected.

The case group included exposed newborns born to mothers infected by SARS-CoV-2 during pregnancy (RT-PCR or positive IgM). The control group included unexposed neonates with no maternal infection with the SARS-CoV-2 virus during pregnancy, no symptoms, and negative IgG and IgM serology at the end of pregnancy. Unexposed control subjects had negative IgG serology at 6 months of adjusted chronological age. Exclusion criteria for the study sample were evidence or confirmation of genetic syndromes; suspected or confirmed other congenital infections, such as toxoplasmosis, syphilis, rubella, herpes, Chagas, and Zika; discontinuation of clinical follow-up before the age of 2 years.

2.2. Neuroimaging data

The study groups were evaluated for morphometric, hemodynamic, and cerebral tissue elasticity parameters using high-frequency ultrasonography. A cranial ultrasound scan (CUS) was performed through the anterior fontanelle at 6 months of adjusted chronological age and repeated 4 weeks later at a follow-up exam in case of abnormal findings at the first CUS. Further examinations were planned thereafter, if indicated, according to an individualized schedule based on the persistence of abnormal findings and their clinical correlation. Only data from the first ultrasound scan of each infant were considered for the purpose of statistical analysis. All CUS were performed or supervised by the same operator (DA). A Philips Affiniti 70 ultrasound system, equipped with a 5–7.5 MHz convex probe

and a 5–18.0 MHz linear probe, was used for CUS studies, divided into the following modalities:

- Cranial ultrasound scan and Doppler of the intracranial arteries —pericallosal artery, middle cerebral artery, and basilar artery; Doppler velocimetry data were analyzed for each individual artery. Absolute values of resistance (RI) and pulsatility index (PI) for blood flow were compared in both groups (exposed vs. control). Images were obtained at the same standard windows over the anterior fontanelle, temporal bone, and suboccipital zone.
- Elastography of the brain parenchyma: scans were performed using ARFI (Acoustic Radiation Force Impulse) and SWE (Shear-wave Elastography) software, which is directly integrated into the ultrasound system where the shear wave is located, allowing the operator to select the region of interest (ROI) for measurement in B-mode and in real-time. The ROIs were divided as follows: deep white matter (DWM), superficial white matter (SWM), basal ganglia (BG), represented by caudate nuclei and thalamus, corpus callosum (CC), and cortical gray matter (CGM) in the frontal lobe. All measurements were repeated at three different locations in the same type of zone and the same slice of view. The archived data represent the mean value of the measurements.

Tissue elasticity was estimated, and the velocity of the shear wave in the brain parenchyma was calculated from the displacement of transverse waves, where the velocity of the shear wave is directly proportional to the local tissue stiffness. The results were expressed in meters per second (m/s) and automatically converted to kilopascals (KpA), with the shear wave propagation velocity being proportional to the square root of the tissue elasticity [$E = 3\text{pc}^2$].

2.3. Data storage

Study records were stored using alphanumeric codes in the REDCap (Research Electronic Data Capture) platform, with access restricted to approved research personnel.

2.4. Statistical analysis

Continuous variables were described as mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were expressed as frequencies and percentages. The prevalence of total abnormalities was evaluated for each category and compared with its prevalence in the control and SARS-CoV-2-exposed groups. A Mann-Whitney *t*-test or ANOVA were used to compare the mean values of imaging parameters.

The neuroimaging parameter means were compared between groups (SARS-CoV-2 exposed vs. controls) using an analysis of covariance (ANCOVA) model. In the ANCOVA model, the neuroimaging parameter measures (RI and PI for Doppler; "E" coefficient/Young's modulus for elastography ROIs) were considered dependent variables, the group (SARS-CoV-2 exposed vs. unexposed) was considered the independent variable, and the measures of GA (gestational age) and BW (birth weight) were considered covariates. A significance level of $p < 0.05$ was considered. Study participants were also grouped into two different categories based on their GA (pre-term and term, considering the cut-off at 37 weeks) and BW (low birth weight and adequate birth weight, considering the cut-off at 2,500 g).

A Cochran-Armitage trend test and Pearson correlation were used to evaluate trends or associations of results between Doppler and cranial ultrasound scans. p-value < 0.05 was considered significant. Analyses were performed using SAS v. 9.4 (SAS Institute, Inc., 2016).

2.5. Ethical approval and informed consent

The study was approved by the Research Ethics Committee of the School of Medicine of the University of Brasilia (Certificate Number C.A.A.E 32359620.0.0000.5558). The protocol was also registered in the Brazilian Registry of Clinical Trials. All pregnant women participating in the study gave informed consent. Likewise, the participation of the children in the pediatric arm required the signed, informed consent of their mothers. The 6-month reports on the status of the study and its partial results are available to the Institutional Research Ethics Committee and can be consulted upon request.

3. Results

3.1. Overview of enrolled subjects

The initial screening included 295 volunteers, sorted by hospital unit, gender, age, and trimester of maternal infection. Two subjects withdrew from the study after the initial phase. Of the 293 subjects evaluated, 74 were excluded due to: (a) loss of follow-up ($n = 72$) and (b) diagnosis of congenital infection ($n = 2$). After exclusions, the total sample included 219 participants, consisting of 201 subjects with documented maternal SARS-CoV-2 infection [exposed group; birth age = 39 ± 2.9 weeks (mean ± SD); 56.6% female] and 18 subjects not exposed to SARS-CoV-2 infection [control group; birth age = 39 ± 2.8 weeks (mean ± SD); 53.0% female]. Gestational age at birth ranged from 33 to 42 weeks (mean 38.1 ± 1.8 weeks), and birth weight ranged from 1,525 to 4,418 g (mean 3,127 ± 535 g).

Concerning maternal diseases prior to pregnancy being affected by COVID-19, 16 patients (7%) had a previous history of systemic arterial hypertension, 3 (1.3%) reported pre-eclampsia, and 15 (6.8%) were affected by pregestational diabetes. A total of 15 patients had a history of pulmonary disease (6.8%), including asthma, and six had heart disease (2.7%).

Considering the clinical characteristics of the control group, the mean age at birth is 38.8 weeks of gestation, with a standard error of ±0.41 w; mean birth weight for controls is 3,277 g, with a standard error of ±107 g; mean head circumference is 35 ± 0.1 cm. The median and interquartile range (IQR) values for the

first- and fifth-minute APGAR scores in the control group are 8 (IQR: 7–8) and 9 (IQR: 9–9), respectively. With our cut-offs of 37 weeks for prematurity and 2,500 g for low birth weight, we have 16.6% (3) pre-term and 11.1% (2) low-birth weight individuals in the control group; the case group has similar frequencies with 14.8% (26) pre-term and 16.5% (29) low-birth weight individuals. Among the comorbidities found within the groups, the most frequent were anemia, bronchospasm, malnutrition, obesity, rhinitis, dermatitis, cow's milk protein allergy (CMPA), and gastroesophageal reflux disease (GERD). A supplemental table in **Appendix C** is provided for reference, demonstrating that groups display a similar profile of comorbidities.

3.2. Findings by imaging modality

3.2.1. Grayscale ultrasonography (structural US)

An association was found between maternal SARS-CoV-2 infection and white matter involvement in their children, with increased echogenicity in grayscale studies. Among the 201 examinations performed in the case group, 18 examinations showed abnormalities in B-mode analysis (8.9%), with deep white matter disease in the totality of these 18 abnormal cases (100%). To a lesser extent, we also saw mild alterations in the basal ganglia (caudate nuclei and thalamus), with abnormal caudothalamic echogenicity in 2 (11.1%) of 18 abnormal B-mode cases, concurrent with the deep white matter findings.

Supplementary Figure A1 summarizes the three main planes for cranial image acquisition and ultrasonographic analysis of deep white matter changes. It also shows CUS B-mode and Doppler velocimetry studies, analyzing three major intracranial arteries (the middle cerebral, pericallosal, and basilar arteries).

An equally significant finding of the morphometric US studies was the persistence of increased echogenicity in the affected areas at the routine second-look ultrasound study, performed 4 weeks after the initial study, in all the abnormal cases. On re-evaluation, it was possible to characterize the clear extension of the affected areas, with additional abnormalities in the basal ganglia—in total, the caudate nuclei and thalami. It is also noteworthy that there were no individuals in the control group (18 out of 219) with grayscale ultrasound alterations.

3.2.2. Hemodynamic abnormalities (Doppler velocimetry)

In the exposed group, 21 out of 201 (10.4%) subjects presented with abnormal hemodynamic patterns, showing a reduction in the resistance (RI) and pulsatility (PI) indices in the blood flow of the major intracranial arteries. We conducted separate analyses of three main intracranial arteries: the middle cerebral artery, the pericallosal artery, and the basilar artery, the former two representing hemodynamic parameters for the anterior intracranial circulation, and the basilar artery velocimetry as an estimate of posterior circulation flow data.

Supplementary Figures A2–A4 demonstrate the Doppler velocimetric scan with spectral curves for the analysis of the flow of three major intracranial arteries (middle cerebral, pericallosal, and basilar arteries).

A significant trend of reduction in both resistance and pulsatility indices of arterial intracranial flow in SARS-CoV-2-exposed children were observed for both anterior and posterior circulation arteries, which was positively correlated with the severity of maternal infection. Significant decreases in RI and PI were found in cases of critical SARS-CoV-2 gestational infection, with mean PI values of 1.09 for the MCA (middle cerebral artery), 0.98 for the PA (pericallosal artery), and 1.04 for the BA (basilar artery).

Table 1 shows the neuroimaging parameters according to the severity of maternal infection (COVID-19 categories according to WHO classification).

When both analyses, mode-B ultrasound, and Doppler scan findings, were integrated and cross-matched with the categories of maternal infection severity, a positive correlation of abnormal neuroimaging results that increased proportionally with the severity of maternal infection, and a peak of abnormal neuroimaging results in children whose mothers had critical SARS-CoV-2 infection during pregnancy could be identified. These data are summarized in **Table 2**.

A second trend in the hemodynamic data was identified in this analysis, related to the duration of SARS-CoV-2 infection during pregnancy. A significant reduction in both the resistance and pulsatility indices of intracranial arterial flow positively correlated with the last trimester of maternal SARS-CoV-2 infection, as shown in **Table 3**.

TABLE 1 Imaging parameters distributed according to the severity of maternal infection (COVID-19 categories according to WHO classification).

Variable[a]	COVID-19 severity scale—WHO			ANOVA	Multiple comparisons *p*-value*		
	Mild ($n = 165$)	Severe ($n = 23$)	Critical ($n = 8$)	*p*-value	Mild to severe	Mild to critical	Severe to critical
MCA RI	0.77 ± 0.09	0.75 ± 0.10	0.64 ± 0.14	0.0011	0.8394	0.0010	0.0260
MCA PI	1.64 ± 0.50	1.47 ± 0.38	1.09 ± 0.45	0.0039	0.3789	0.0064	0.1713
Pericallosal RI	0.70 ± 0.08	0.68 ± 0.10	0.61 ± 0.09	0.0062	0.7004	0.0070	0.1185
Pericallosal PI	1.29 ± 0.31	1.19 ± 0.25	0.98 ± 0.24	0.0113	0.4744	0.0181	0.2833
Basilar RI	0.72 ± 0.07	0.69 ± 0.09	0.64 ± 0.09	0.0032	0.1692	0.0093	0.3330
Basilar PI	1.34 ± 0.29	1.24 ± 0.28	1.04 ± 0.28	0.0121	0.4389	0.0208	0.3229

MCA, middle cerebral artery; RI, resistance index; PI, pulsatility index.
[a]values expressed as mean ± standard error.
*p-values for multiple comparisons adjusted with Bonferroni correction.

TABLE 2 Neuroimaging parameters are distributed according to the COVID-19 severity scale—WHO classification.

Variable[a]	COVID-19 severity scale—WHO[a]			Pearson correlation (CI 95%)	*p*-value*
	Mild (*n* = 166)	Severe (*n* = 23)	Critical (*n* = 8)		
Intracranial Doppler				0.23 (0.06; 0.40)	<0.001
Abnormal	11 (6.63)	5 (21.74)	5 (62.50)		
Normal	155 (93.37)	18 (78.26)	3 (37.50)		
Ultrasonography				0.24 (0.06; 0.42)	<0.001
Abnormal	9 (5.42)	5 (21.74)	4 (50.00)		
Normal	157 (94.58)	18 (78.26)	4 (50.00)		

[a]Values expressed in frequency (%).
*p-value calculated with the Cochran-Armitage trend test.

TABLE 3 Neuroimaging parameters (ultrasound B-mode and Doppler analysis) distributed according to the trimester of SARS-CoV-2 infection during pregnancy.

Variable[a]	Gestational trimester of SARS-CoV-2 infection[a]					
	1st (*n* = 27)	2nd (*n* = 58)	3rd (*n* = 95)	Peripartum (*n* = 21)	Pearson Correlation (CI 95%)	*p*-value*
Intracranial arteries Doppler					0.43 (0.32; 0.54)	<0.001
Abnormal	0 (0.00)	1 (1.72)	6 (6.32)	14 (66.67)		
Normal	27 (100.00)	57 (98.28)	89 (93.68)	7 (33.33)		
Ultrasound B-mode					0.41 (0.30; 0.53)	<0.001
Abnormal	0 (0.00)	1 (1.72)	4 (4.21)	13 (61.90)		
Normal	27 (100.00)	57 (98.28)	91 (95.79)	8 (38.10)		

[a]Values expressed in frequency (%).
*p-value calculated with the Cochran-Armitage trend test.

The hemodynamic evaluation data show a significant correlation between the resistance/pulsatility indices in the main intracranial arteries and the trimester of maternal infection, with the highest proportional frequency of abnormal results observed in cases of peripartum infection (defined as a period equal to or less than 14 days between infection with SARS-CoV-2 and the date of delivery). Among the pregnant women infected during this period, 66% had abnormal Doppler velocimetry, and nearly 62% had abnormal cranial ultrasound in grayscale.

3.2.3. Elastography abnormalities (shear-wave ultrasound-based)

The functional studies based on shear-wave elastography were performed in five regions of interest (ROIs) and "E" cut-off references were adopted according to previous recent literature (6–8), as there is no definitive normality parameter for elastography studies in the pediatric brain.

A significant relationship was found between maternal exposure to SARS-CoV-2 and elastography changes, mainly in the cerebral deep white matter and basal ganglia, in terms of stiffness alterations, with a decrease of the elastic modulus (*E*) in the SARS-CoV-2-exposed group when compared to controls. Table 4 shows these findings categorized by ROIs.

The SARS-CoV-2 group had significantly lower "*E*" coefficients in specific brain areas, including the deep/periventricular white matter and the splenium of the corpus callosum. The basal ganglia (caudate nuclei and thalamus), superficial white matter, and cortical gray matter also showed stiffness variations associated with SARS-CoV-2 exposure, although to a lesser extent.

TABLE 4 Neuroimaging parameters of children distributed between the group exposed to SARS-CoV-2 infection during gestation (cases) and the non-exposed (control) group, according to the specific regions of interest (ROIs) for elastography analysis: deep white matter, frontal white matter, caudate/thalamus, corpus callosum, and frontal cortex.

Variable[a]	Groups		*p*-value*
	Cases (*n* = 201)	Control (*n* = 18)	
Elastography—DWM	3.98 ± 0.62	7.76 ± 0.77	<0.001
Elastography—FWM	3.31 ± 0.59	4.69 ± 0.85	<0.001
Elastography—caudate/thalamus	5.45 ± 0.64	6.46 ± 0.96	<0.001
Elastography—corpus callosum	4.53 ± 0.39	7.93 ± 0.88	<0.001
Elastography—frontal cortex	5.62 ± 0.57	6.59 ± 0.66	<0.001

DWM, deep white matter; FWM, frontal white matter.
[a]Values expressed in kilopascal, as mean ± standard error.
*p-value calculated by Mann-Whitney test.

A significant dose-response relationship was found between exposure to SARS-CoV-2 during pregnancy and the presence of neuroimaging abnormalities, including grayscale, Doppler, and elastography modalities.

The neuroimaging parameter means were also compared between groups (SARS-CoV-2 exposure vs. non-exposure) using an analysis of covariance (ANCOVA) model. In this ANCOVA model, the neuroimaging parameter measures (hemodynamic indices and elastic modulus) were considered dependent variables, the group (SARS-CoV-2 exposure vs. non-exposure) was considered the independent variable, and the measures of GA (gestational age) and BW (birth weight) were considered covariates.

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TABLE 5 Neuroimaging parameters of infants distributed between the group exposed to SARS-CoV-2 infection during gestation (cases) and the unexposed group (control), controlled by GA (gestational age) and BW (birth weight), according to the specific regions of interest (ROIs) for elastography analysis: deep white matter, frontal white matter, caudate/thalamus, corpus callosum, and frontal cortex; *p*-value calculated by ANCOVA model.

Variable	Groups—mean value[a] ± standard error		Comparison between groups	
	Cases (*n* = 201)	Control (*n* = 18)	Difference [CI 95%]	*p*-value*
MCA—RI	0.76 ± 0.01	0.79 ± 0.01	−0.03 [−0.07; −0.00]	0.0451
MCA—PI	1.59 ± 0.03	1.65 ± 0.08	−0.04 [−0.08; −0.00]	0.0434
Pericallosal artery—RI	0.70 ± 0.00	0.73 ± 0.01	−0.03 [−0.06; −0.00]	0.0277
Pericallosal artery—PI	1.26 ± 0.02	1.40 ± 0.05	−0.14 [−0.25; −0.03]	0.0123
Basilar artery—RI	0.71 ± 0.00	0.73 ± 0.02	−0.02 [−0.04; 0.01]	0.2324
Basilar artery—PI	1.31 ± 0.02	1.32 ± 0.07	−0.01 [−0.14; 0.14]	0.9585
Elastography—DWM	3.98 ± 0.04	7.77 ± 0.11	−3.80 [−4.03; −3.57]	<0.001
Elastography—FWM	3.31 ± 0.04	4.69 ± 0.11	−1.37 [−1.60; −1.14]	<0.001
Elastography—caudate nucleus/thalamus	5.46 ± 0.05	6.45 ± 0.12	−0.99 [−1.24; −0.74]	<0.001
Elastography—corpus callosum	4.56 ± 0.03	7.92 ± 0.08	−3.38 [−3.56; −3.20]	<0.001
Elastography—frontal cortex	5.61 ± 0.04	6.60 ± 0.10	−0.99 [−1.20; −0.78]	<0.001

Mean values adjusted by ANCOVA model. MCA, middle cerebral artery; RI, resistance index; PI, pulsatility index; DWM, deep white matter; FWM, frontal white matter.
[a]Results are expressed in kilopascals, as mean ± standard error.
**p*-values for comparison between groups were calculated using ANCOVA model, with GA and BW as covariates.

As shown in Table 5, the neuroimaging parameters of the patients present significant differences between the two groups, even after controlling for GA and BW. According to the data, the mean value of deep white matter elasticity in the group exposed to SARS-CoV-2 is 3.98 ± 0.04, while in the group without SARS-CoV-2, it is 7.77 ± 0.11. The difference between the two groups is −3.80 with a 95% confidence interval of [−4.03, −3.57] and a *p*-value of less than 0.001. This means that there is a statistically significant difference between the two groups for this parameter, indicating that patients exposed to SARS-CoV-2 during pregnancy have lower values for deep white matter elasticity compared to those not exposed to SARS-CoV-2. In contrast, the parameters for a single vessel (basilar artery) interestingly did not show a significant difference between the two groups, when adjusted for GA and BW. Considering the basilar artery RI, the difference between the two groups is −0.02 with a 95% confidence interval of [−0.04, 0.01] and a *p*-value of 0.2324.

4. Discussion

4.1. General evidence

A systemic inflammatory response to the SARS-CoV-2 virus and consequent endothelial damage has been implicated in COVID-19 pathogenesis, with replicated evidence in many studies in both biochemical and clinical settings (9–11). Although there is extensive epidemiologic evidence of systemic COVID-19 effects (12, 13), the neurologic consequences of SARS-CoV-2 exposure in the pediatric group are still uncertain, and current evidence is mostly based on case reports (14, 15). It is not clear whether and to what extent the blood-brain barrier functions as a protective factor in blocking inflammatory cytokines (16–19).

Our study provides evidence that SARS-CoV-2 infection during pregnancy may be associated with both structural and functional brain damage in infants. The most recurrent findings were characterized in the cerebral deep white matter, although all other ROIs demonstrated some degree of change. These changes were manifested by increased regional echogenicity on B-mode studies, a reduction in the corresponding resistance/pulsatility of intracranial arterial flow, and a decrease in the cerebral elastic modulus. The reduced stiffness in the cerebral tissue, especially in the deep white matter, may represent a decreased amount of tissular myelin in the central nervous system, a crucial element for adequate neurodevelopment in children. Few neuroimaging studies have been conducted in this area with pediatric subjects, so our results provide unprecedented evidence based on structural and functional abnormalities.

4.2. Ultrasonographic findings (gray scale)

Structural neuroimaging scans in our study have repeatedly demonstrated white matter involvement in abnormal cases in SARS-CoV-2-exposed subjects. To date, there are published case series (20, 21) reporting a similar pattern of involvement in COVID-19, but no longitudinally designed studies with SARS-CoV-2-exposed and unexposed control groups correlating neuroimaging findings and clinical follow-up.

Because there is exceptional collateral circulation in the brain vasculature in the neonatal period and early childhood, the pattern of parenchymal involvement in these subjects tends to be less severe in the cortical gray matter (unlike in adults). In response to vascular and/or hypoxic encephalic injury, the deep white matter is one of the first areas of the brain affected during this early period of life (22–24).

This evidence was replicated in our results, as both deep white matter and basal ganglia areas presented as regions of higher echogenicity in abnormal B-mode scans when compared to

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controls (the unexposed group). In our sample, 18 individuals whose mothers were infected by SARS-CoV-2 during pregnancy manifested some degree of white matter disease, of which 16 (88.8%) had exclusive white matter involvement and two (11.2%) subjects had concomitant involvement of deep white matter and cerebral basal ganglia (thalami and caudate nuclei). Another significant finding of the morphometric US studies was the persistence of increased echogenicity in the affected areas at the routine follow-up ultrasound study, performed 4 weeks after the initial scan, in all the abnormal cases. At re-evaluation, it was possible to characterize an increase in the extent of the affected areas in three individuals (16.6%) who evolved from initial exclusive deep white matter lesions to additional abnormalities in the basal ganglia, in total, the caudate nuclei and thalami.

Although the correlation of basal ganglia changes with the clinical COVID-19 syndrome is still unclear, it is thought to play a role in the long-lasting damage that some infants have shown, manifesting as late-onset post-COVID-19 symptoms, with delayed neurological development and failure to achieve neuropsychomotor milestones at specific ages (25, 26).

4.3. Hemodynamics findings (Doppler evaluation)

Our data regarding intracranial blood flow analysis in both groups suggest a relevant trend of decrease in RI (resistance) and PI (pulsatility) indices in the SARS-CoV-2-exposed group when maternal infections occur in the last 14 days of gestation and critical cases. This fact is thought to be a consequence of systemic adaptation to the persistent inflammatory condition that may be present even after the first 14 days of acute viral symptoms (27, 28). Cases of early maternal infection with SARS-CoV-2 during pregnancy, especially in the first and second trimesters, would allow sufficient time for arterial flow autoregulation to settle and the systemic inflammatory response to subside.

Such hemodynamic adaptation findings have been widely reported in the literature for other conditions predisposing to brain injury, such as hypoxic-ischemic injury, metabolic damage, and systemic inflammatory conditions (SIRS—systemic inflammatory response syndrome) (29, 30), generally indicating situations in which the brain has increased metabolic demands and a significant increase in intracranial blood flow is required. In fetal life, an analogous situation is classically demonstrated in cases of fetal intrauterine growth-restriction (IUGR), when the fetal arterial flow is redirected to the intracranial circulation to the detriment of visceral and peripheral flow (31–33).

Unlike other viral infections with the well-known transplacental transmission, such as human cytomegalovirus (CMV), rubella virus, parvovirus B19, and Zika virus (ZIKV), the worst pregnancy outcomes in SARS-CoV-2 infection were observed in late-stage pregnancies. This finding is consistent with the current literature, as current evidence does not demonstrate that SARS-CoV-2 represents efficient transplacental virus transmission or direct fetal neuronal damage (34, 35).

4.4. Elastography findings (shear-wave elastography assessment)

To our knowledge, no previous study has assessed elastography parameters of the brain parenchyma in infants exposed to SARS-CoV-2 during pregnancy. The few publications in the pediatric literature include small case series of healthy individuals aimed at suggesting standard elastography values for normal brain parenchyma in neonates (36, 37). Other similar studies have been conducted in mice with anatomopathological correlations (38, 39). Experiments in mice achieved a significant level of agreement with human brain values, presumably related to the very similar elasticity coefficients/energy densities (p) of mouse and human brains.

When the elastography data of our study groups were analyzed, significant differences were found between SARS-CoV-2-exposed newborns and the unexposed group in terms of the elastic modulus of the brain parenchyma. All regions of interest (ROIs) showed a reduction in the elasticity coefficient/Young's modulus (E) in the SARS-CoV-2-exposed group.

The elastography pattern differences between both groups were more pronounced in the DWM deep white matter zone (ROI number 1) when compared to other regions of analysis such as subcortical white matter and the frontal cortex. A plausible hypothesis is related to differences in the tissular composition of these regions, with a predominance of myelin in the deep white matter (40). Considering also the age of the subjects (6 months of adjusted chronological age), our ROI at the DWM was expected to be myelinated at this stage, different from the subcortex or frontal cortical zones (41–43). These elements suggest that brain findings related to SARS-CoV-2 exposure during pregnancy may be due, to some extent, to changes in the amount of myelin in the cerebral tissue, knowing that those with less myelin present a decrease in their elasticity coefficients, corresponding to a reduction in stiffness. Another possible mechanism could be mild intra-myelinic edema, in which the inflammation causes an increased water content in the cerebral tissue, thus leading to a decrease in tissue stiffness.

Our findings are consistent with recent studies investigating the impact of SARS-CoV-2 infection during pregnancy on pediatric neurodevelopment. Regarding neuroimaging, a study published in October 2021 aimed to assess the association between maternal SARS-CoV-2 infection during pregnancy and offspring brain development using MRI scans (44). The study followed 55 infants born to mothers with SARS-CoV-2 infection during pregnancy. The researchers found that infants born to mothers with SARS-CoV-2 infection during pregnancy had reduced cortical thickness in the left superior temporal gyrus, which is an important brain region for language and social communication. Abnormal cortical thickness in this region has been associated with neurodevelopmental conditions such as autism spectrum disorders. The study suggests that maternal SARS-CoV-2 infection during pregnancy may affect offspring brain development, particularly in brain regions important for language and social communication.

Protocols with a more clinical focus included a study published in January 2022 (45) that followed 205 children born to mothers with SARS-CoV-2 infection during pregnancy and found that children born to mothers with SARS-CoV-2 infection during pregnancy had an increased risk of developmental delay at 12 months of age compared to children born to mothers without SARS-CoV-2 infection. Another study published in August 2021 (46) found that children born to mothers with severe or critical COVID-19 during pregnancy had a higher risk of cognitive, motor, and language developmental delays at 6 months of age compared to children born to mothers without COVID-19. The study followed 150 infants born to mothers with COVID-19 and 150 infants born to mothers without COVID-19.

It is worth noting that these studies have limitations, and more research is needed to fully understand the potential effects of SARS-CoV-2 infection during pregnancy on pediatric neurodevelopment. However, the findings suggest that healthcare providers should closely monitor children born to mothers with SARS-CoV-2 infection during pregnancy for any signs of developmental delays or neurodevelopmental disorders.

4.5. Limitations

Causal associations between SARS-CoV-2 infection and adverse perinatal outcomes have been suggested in clinical studies but have not been definitely established, as there are many potential confounding factors involved. Among these, we should emphasize that mothers infected by SARS-CoV-2 during pregnancy are often prone to gestational complications, including adverse birth conditions, preterm labor, and maternal and neonatal hypoxia—factors that may themselves lead to CNS damage. Controlling all of these factors can be challenging. Our study attempted to control for some of these possible biases with covariance analysis techniques. However, many characteristics related to clinical maternal status, such as gestational hypertension, diabetes, previous lung disease, and obesity, persisted in our sample for both groups and may affect neurodevelopmental outcomes in infants. It is also relevant to consider that most of our sample was composed of outpatients, so the severity of maternal infection was predominantly mild to moderate, and there was a quantitative disproportion between case and control groups, given the context of multiple lockdowns and subsequent SARS-CoV-2 vaccination—the latter being one of the exclusion criteria for the control group. We acknowledge the substantial difference in the sample size between the cases and controls, and the possibility of introducing bias as a result. Because infant outcomes of maternal SARS-CoV-2 exposure during pregnancy are poorly defined to date, an accurate prospective sample size estimation for cases and controls was not feasible. However, a *post hoc* analysis was performed to estimate the number of controls needed to maintain a probability of error (alpha) of 0.05 with a power of 0.8 using the relative frequency of abnormal imaging findings in the cases. We used a likelihood ratio test to estimate the sample size needed for controls and found that $N = 9$. Thus, we believe that the control group in our study is sufficient for our research questions. Furthermore, the prospective recruitment of our controls involved randomly selecting individuals from a large representative population in our universal public health system.

5. Conclusion

SARS-CoV-2 infection during pregnancy is associated with encephalic changes in a relevant proportion of cases, predominantly affecting the cerebral deep white matter (DWM). The characteristic SARS-CoV-2-related pediatric leukopathy is manifested in neuroimaging with increased echogenicity and decreased elasticity coefficients in the DWM, i.e., reduced stiffness. These findings open up a spectrum of research possibilities regarding their effects on fetal, neonatal, and childhood health. The description of the consequences of infection in long-term follow-up may provide a better understanding of the disease and its impact on the central nervous system.

Future research using correlated axial methods, such as magnetic resonance imaging and tractography, may contribute to predicting brain areas more vulnerable to SARS-CoV-2-related encephalopathy and delineating regions with a propensity for decreased myelination. By understanding the neuroimaging correlates of SARS-CoV-2 infection in the perinatal period, this study could provide a more complete picture of the presentation pattern in the brain of SARS-CoV-2-exposed individuals during early childhood. The characterization of pediatric brain areas with a higher risk of neurological damage following maternal SARS-CoV-2 infection will allow the evaluation of clinical correlates and the early prevention of neurodevelopmental sequelae.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of the University of Brasilia School of Medicine (Certificate Number 32359620.0.0000.5558). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Study design: DA, FM, GF, MC, LS, CA, and LM. Advisory committee: LL, TR, PK, LE, AZ, AS, and ON. Funding

acquisition: LE, AZ, CG, OM-F, and LM. Sample collection, clinical appointments, and data collection: DA, FM, GF, MC, and LS. Data analysis: DA, FM, LL, TR, CA, and LM. Writing and revision of the manuscript: DA, FM, LL, TR, CA, and LM. All authors have participated sufficiently in the work to take responsibility for its content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1194114/full#supplementary-material.

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An evaluation of the association between lockdown during the SARS-CoV-2 pandemic and prematurity at the Nice University Hospital

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Aim: To study the association between lockdown in France due to the SARS-CoV-2 pandemic and premature births at the Nice University Hospital.
Methods: Data concerning neonates born at the level III maternity of the Nice University Hospital and immediately hospitalised in the neonatal reanimation unit or the neonatology department of the hospital with their mothers between the 1st of January 2017 and the 31st of December 2020, included.
Results: We did not find a significant decrease in the global number of premature births <37 weeks of gestation, in low weight at birth or a significant increase in stillbirths during lockdown compared to a period with no lockdown. The profiles of the mothers and their newborns were compared when birth occurred during lockdown vs. no lockdown.
Conclusion: We did not find any evidence of an association between lockdown and prematurity at the Nice University Hospital. This result is in agreement with meta-analyses published in the medical literature. The possible decrease in factors of risk of prematurity during lockdown is controversial.

KEYWORDS
SARS-CoV-2 pandemic, lockdown, prematurity, low weight at birth, stillbirth

1. Introduction

Prematurity is a major public health problem. Premature births represent 75% of perinatal mortality and more than half of infantile morbidity over the long term. Between 50,000 and 60,000 infants are born prematurely each year in France (1).

There are many factors of risk of prematurity. They can be related to obstetrical elements, maternal history and environmental factors. Some of the factors of risk changed during lockdown due to the SARS-CoV-2 virus, in particular imposed inactivity, atmospheric changes, changes to daily living and an increase in hygiene. France went into lockdown as of Tuesday 17th of March 2020 up to Sunday the 10th of May 2020, included. All nurseries, schools, universities have been closed as well as restaurant and business not essential. Outdoor gatherings, family or friendly reunions were no longer allowed. Teleworking has been promoted and barrier measures have been put in place (wearing a mask, social distancing, hygine promotion) (2).

The main aim of our study was to examine the association between lockdown and the birth of premature newborns in the general population at the level III maternity of the University Hospital of Nice.

2. Materials et methods

2.1. Description of the study

An observational retrospective and monocentric study was performed at the neonatal reanimation unit and neonatal department of the University Hospital of Nice, a level III maternity.

The hospital's computer databases and written reports of biological results and hospitalisation were used to collect data.

2.2. Criteria of inclusion

All newborns including full-term infants born at the University Hospital of Nice immediately admitted into the neonatal reanimation unit or neonatal department between the 1st of January 2017 and 31st of December 2020 were included (Figure 1).

2.3. Data collection

The data included information concerning mothers and newborns. The information about the mother included: age, history of prematurity, injection of complete maturative antenatal corticosteroid therapy (two doses), antenatal administration of magnesium sulphate, mode of delivery (vaginal or caesarean) and the context of birth. The latter included risks of premature birth, premature rupture of membranes, vascular causes such as pre-eclampsia, metrorrhagia, suspicion of chorioamnionitis and other causes. The information about the newborn included: the weight and term of birth, the sex, administration of surfactant, the presence of broncho-pulmonary dysplasia defined as the need of supplementary oxygen for premature babies after 28 days of life, intra-ventricular hemorrage according to grade 3 (intra-ventricular hemorrage with dilation occupying more than 50% of the ventricule) and grade 4 Papile classification (intra-ventricular hemorrage with associated parenchymal lesions) (3), periventricular leucomalacia determined by lesions of the periventricular white matter, ulcero-necrotic enterocolitis characteristic of necrosis of the digestive wall classified according to the modified Bell score (stage 2a and 3b) (4), retinopathy of prematurity characterised by a proliferative disorder of the vessels of the retina, patent ductus arteriosus, microbial infection identified with a sample (blood or cerebrospinal fluid culture) and the occurrence or not of death.

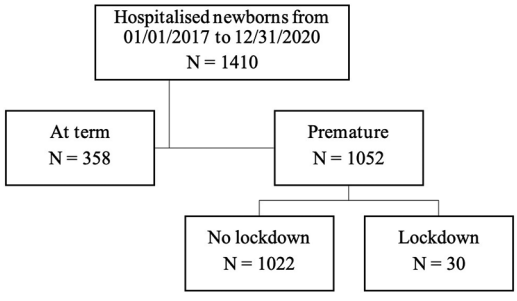

FIGURE 1
Flow chart.

2.4. Methods and statistical analysis

The total number of births and the term of the pregnancies were first analysed in a descriptive way from the 1st of January 2017 to the 31st of December 2020. The number of premature births and the weight of the newborns hospitalised per year was then noted. The incidence of prematurity, the low weights at birth and stillbirths were then compared for the period of lockdown vs. no lockdown. Finally, the profiles of the newborns and their mothers were compared during lockdown (from Tuesday 17th of March to Sunday 10th of May 2020, included) vs. the years 2017–2019 and vs. the date to date period (from 17th of March to the 10th of May for the years 2017, 2018 and 2019). We made comparisons with two different time periods to avoid seasonal variables. The descriptive analysis gave the frequencies and percentages for the qualitative variables as averages and standard deviations. The univariate analyses used the Pearson's chi-square test (or the Fisher's exact test) for qualitative variables and the Anova (or Kruskal-Wallis rank test) for quantitative variables where the mean is presented with range. Statistical analysis used R software (version 4.1.2). All tests were bilateral and a p-value <0.05 was considered as statistically significant.

2.5. Legal information

This study was referred to the « Comité d'Éthique pour les Recherches Non Interventionnelles ». A favourable response was obtained on the 1st of June 2021, agreement n°2021-034.

3. Results

Despite substantial variation in the number of hospital stays each month, fluctuation was random, a regular seasonal cycles was not observed (Figure 2). The number of premature births <37 weeks of gestation decreased continually each year in a non significant way, giving a lower frequency in 2020 ($N = 227$). We found that this non significant decline was mainly related to « severely premature » newborns ($N = 59$ in 2020 vs. $N = 92$ in 2017, $N = 89$ in 2018, $N = 76$ in 2019). Significant variation in the weights of the newborns was found for the different periods (Table 1). We did not find a significant decrease in either the frequency of prematurity <37 weeks of gestation or low weights at birth during

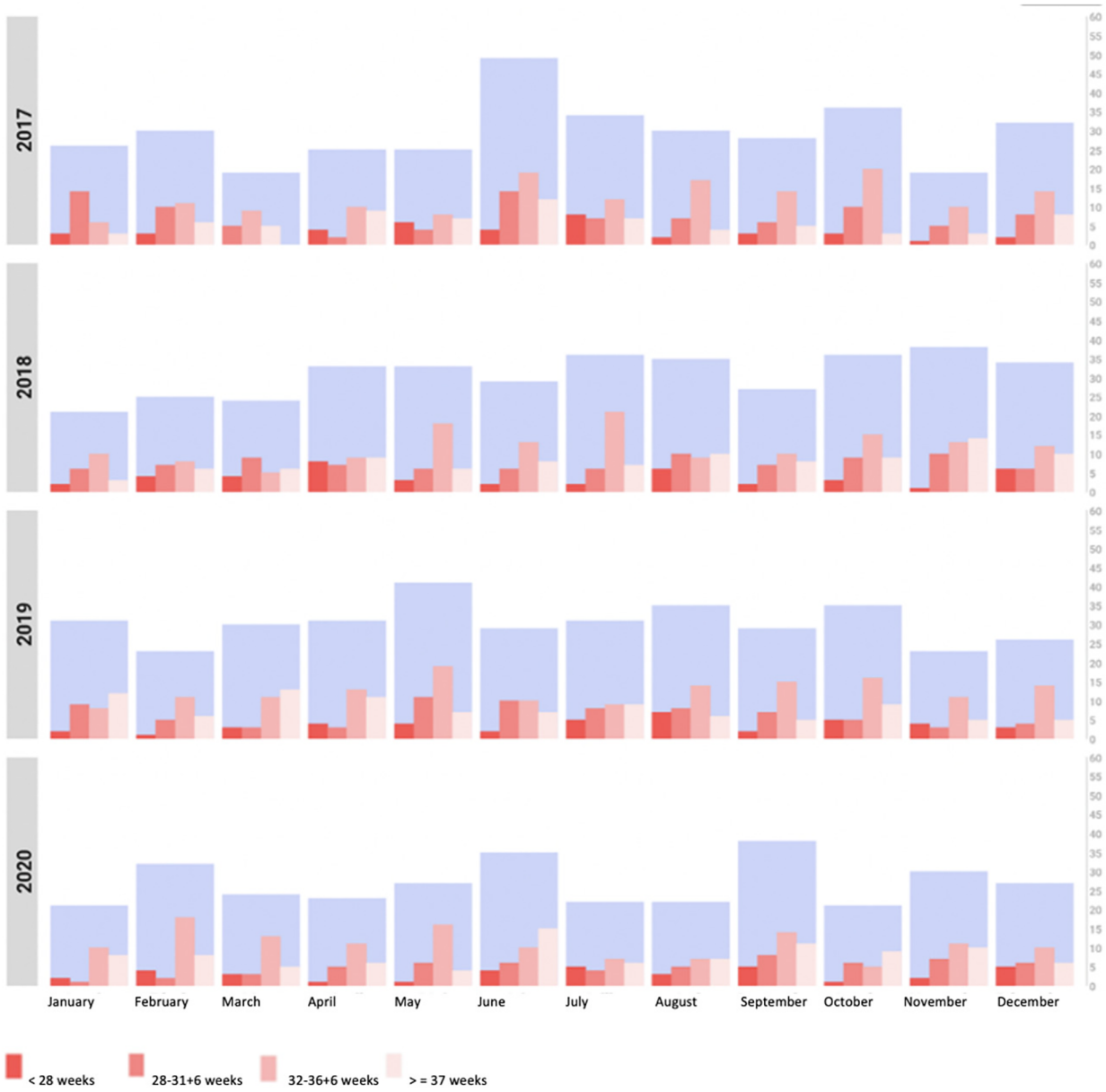

FIGURE 2
Total births and births according to the term in 2017, 2018, 2019 and 2020.

lockdown compared to the average for 2017–2019 ($p = 0.579$ for term pregnancies, $p = 0.392$ for <1,000 g, $p = 0.698$ for <1,500 g) or date to date $p = 0.689$ for term pregnancies, $p = 0.197$ for <1,000 g, and $p = 0.504$ for <1,500 g). There was no significant increase in the number of stillborns during lockdown compared to no lockdown $p > 0.99$) (Table 2). When we compared the profiles of the mothers and newborns according to the term in lockdown vs. no lockdown we noted a significant decrease in the frequency of bronchopulmonary dysplasia of the severely premature, born before 28 weeks of gestation $p = 0.049$) but only when compared to the average for 2017–2019; this significant difference was not found when compared to the date to date period $p = 0.076$). In addition, the profiles of the mothers and newborns were comparable for the different periods (Tables 3, 4).

4. Discussion

This study did not reveal any evidence of a significant decrease in either prematurity or low birth weights during lockdown. There was no significant increase in the number of stillbirths. There was no significant difference in the profiles of the mothers or newborns. The collection of information is limited by the retrospective nature of the study since some of the data was missing or absent, which leads to a degree of bias regarding the information. Some of the absent information concerned maternal risk factors such as the preconception body mass index, the marital status, the economic status and level of education. In addition, the study lacked power due to the low number of individuals included, despite the collection of date over four years. Thus, the monocentric nature

TABLE 1 Frequency of prematurity in the general population and birth weight of newborns hospitalised in the unit according to the year.

	2017 (*N* = 353)	2018 (*N* = 371)	2019 (*N* = 364)	2020 (*N* = 322)	Total (*N* = 1410)	*p*–value
Term at birth	32.93 (24.00–42.00)	33.30 (24.00–42.00)	33.35 (24.00–42.00)	33.50 (23.00–42.00)	33.27 (23.00–42.00)	0.379
Grouped term at birth						0.143
<28 weeks	39 (11.0%)	43 (11.6%)	42 (11.5%)	36 (11.2%)	160 (11.3%)	
28–31 weeks	92 (26.1%)	89 (24.0%)	76 (20.9%)	59 (18.3%)	316 (22.4%)	
32–36 weeks	150 (42.5%)	143 (38.5%)	151 (41.5%)	132 (41.0%)	576 (40.9%)	
≥37 weeks	72 (20.4%)	96 (25.9%)	95 (26.1%)	95 (29.5%)	358 (25.4%)	
<28 weeks	39 (11.0%)	43 (11.6%)	42 (11.5%)	36 (11.2%)	160 (11.3%)	0.995
<32 weeks	131 (37.1%)	132 (35.6%)	118 (32.4%)	95 (29.5%)	476 (33.8%)	0.156
<37 weeks	281 (79.6%)	275 (74.1%)	269 (73.9%)	227 (70.5%)	1,052 (74.6%)	0.053
Birth weight (g)	1,920 (530.00–5,160.00)	2,030.35 (520.00–5,302.00)	2,006.61 (500.00–4,812.00)	2,062.57 (400.00–4,508.00)	2,004.09 (400.00–5,302.00)	0.209
Birth weight (scale)						0.549
ELBW	42 (11.9%)	42 (11.3%)	49 (13.5%)	45 (14.0%)	178 (12.6%)	
VLBW	82 (23.3%)	76 (20.5%)	76 (20.9%)	52 (16.1%)	286 (20.3%)	
LBW	148 (42.0%)	151 (40.7%)	136 (37.4%)	131 (40.7%)	566 (40.2%)	
NBW	80 (22.7%)	102 (27.5%)	103 (28.3%)	94 (29.2%)	379 (26.9%)	

ELBW, extremely low birth weight <1,000 g; LBW, low birth weight <2,500 g; VLBW, very low birth weight <1,500 g; NBW, normal birth weight >2,500 g.

of the study does not allow generalisation of the results, which limits the external validity. However, the strength of the study lies in the exhaustive collection of hospitalised births admitted into the critical care neonatal unit and neonatology department of the Nice University Hospital during lockdown as well as the uniformity of the data and the collection of the number of stillborns. The number of stillborns was not different between periods and did not have an impact on prematurity.

The results are in agreement with some of the published literature and in particular with some meta-analyses concerning this subject, including the meta-analyses of Vaccaro et al. (5), Chmielewska et al. (6), and Yang et al. (7). Several studies showed that lockdown did not result in a decrease in prematurity, including in France (8), Spain (9), Sweden (10), Israel (11), the United States of America (12), the United Kingdom (13), and China (14). A meta-analysis by Vaccaro *et al.* evaluated the impact of lockdown on prematurity, low birth weight <2,500 g and stillbirths but did not report an association between lockdown and these issues (5). Another meta-analysis by Chmielewska et al. did not find an association between lockdown and prematurity and low birth weight <2,500 g (6). A third meta-analysis by Yang et al. did not find any association between prematurity and lockdown in studies using regional/national data (7). In contrast, the initial published results were in favour of a decrease in prematurity and a low weight at birth during lockdown, notably by studies performed in spring of 2020 in Ireland (15) and Denmark (16). Other studies evaluating the association between prematurity, low birth weight and the number of stillborns performed around the world also found similar results, including in Iran (17), Australia (18), Saudi Arabia (19), Italy (20), Netherlands (21) and Austria (22). Two meta-analyses also demonstrated a decrease of prematurity during lockdown. Calvert et al. showed small reductions in preterm birth in high income and upper middle income countries during the first, second and third months of lockdown (but not in the fourth month) (23). Yao et al. identified a

TABLE 2 Incidence of prematurity, sex, weight and number of stillborns during lockdown (from Tuesday 17th of March to Sunday 10th of May 2020) vs. mean of 2017–2019 and date to date (from the 17th of March to the 10th of May of years 2017, 2018 and 2019).

	Lockdown vs. mean of 2017–2019				Lockdown vs. date to date			
	Lockdown (*N* = 39)	No lockdown (*N* = 1,088)	Total (*N* = 1,127)	*p*-value	Lockdown (*N* = 39)	Lockdown (*N* = 159)	Total (*N* = 198)	*p*-value
Term at birth	33.59 (24.00–40.00)	33.20 (24.00–42.00)	33.21 (24.00–42.00)	0.579	33.59 (24.00–40.00)	33.26 (25.00–42.00)	33.33 (24.00–42.00)	0.689
<28 weeks	2 (5.1%)	124 (11.4%)	126 (11.2%)	0.222	2 (5.1%)	25 (15.7%)	27 (13.6%)	0.084
<32 weeks	12 (30.8%)	381 (35.0%)	393 (34.9%)	0.584	12 (30.8%)	54 (34.0%)	66 (33.3%)	0.705
<37 weeks	30 (76.9%)	825 (75.8%)	855 (75.9%)	0.875	30 (76.9%)	113 (71.1%)	143 (72.2%)	0.465
Sex				0.939				0.704
Boy	22 (56.4%)	95 (55.8%)	117 (55.8%)		22 (56.4%)	95 (59.7%)	117 (59.1%)	
Girl	17 (43.6%)	481 (44.2%)	498 (44.2%)		17 (43.6%)	64 (40.3%)	81 (40.9%)	
Weight <1,000 g	3 (7.7%)	133 (12.2%)	136 (12.1%)	0.392	3 (7.7%)	101 (63.5%)	128 (64.6%)	0.197
Weight <1,500 g	12 (30.8%)	367 (33.8%)	379 (33.7%)	0.698	12 (30.8%)	58 (36.5%)	70 (35.4%)	0.504
				>0.99				>0.99
Nb of total births	452	9,729	10,181		452	1,383	1,835	
Nb of stillborns	9	261	270		9	31	40	

Nb, number.

TABLE 3 Profiles of the mothers and newborns by term during lockdown (from Tuesday 17th of March 2020 to Sunday 10th of May 2020 included) vs. mean of 2017–2019.

	<28 weeks				28–31 ± 6 weeks				32–36 ± 6 weeks			
	Lockdown (*N* = 2)	No lockdown (*N* = 124)	Total (*N* = 126)	*p*-value	Lockdown (*N* = 10)	No lockdown (*N* = 257)	Total (*N* = 267)	*p*-value	Lockdown (*N* = 18)	No lockdown (*N* = 444)	Total (*N* = 462)	*p*-value
Characteristics of mothers and newborns												
Sex				0.782				0.804				0.885
Boy	1 (50%)	74 (59.7%)	75 (59.5%)		6 (60.0%)	144 (56.0%)	150 (56.2%)		10 (55.6%)	239 (53.8%)	249 (53.9%)	
Girl	1 (50%)	50 (40.3%)	51 (40.5%)		4 (40.0%)	113 (44.0%)	117 (43.8%)		8 (44.4%)	205 (46.2%)	213 (46.1%)	
Mother's age	34 (27.00–41.00)	31.03 (19.00–44.00)	31.08 (19.00–44.00)	0.446	33.30 (25.00–41.00)	31.44 (18.00–56.00)	31.51 (18.00–56.00)	0.340	33.35 (24.00–44.00)	31.62 (16.00–49.00)	31.68 (16.00–49.00)	0.232
Premature birth history	0 (0.0%)	12 (9.8%)	12 (9.7.%)	0.641	3 (30.0%)	17 (6.7%)	20 (7.5.%)	0.006	4 (22.2%)	26 (5.9%)	30 (6.5%)	0.007
History of fetal death *in utero*	0 (0.0%)	5 (4.1%)	5 (4.0%)	0.538	0 (0.0%)	7 (2.7%)	7 (2.6%)	0.503	0 (0.0%)	16 (3.6%)	16 (3.5%)	0.090
Complete antenatal corticosteroid therapy	2 (100%)	84 (67.7%)	86 (68.3%)	–	6 (60.0%)	205 (80.1%)	211 (73.9%)	0.270	9 (50.0%)	259 (58.3%)	268 (58.0%)	0.745
Magnesium sulfate	1 (50.0%)	104 (83.9%)	105 (83.3%)	0.202	10 (100.0%)	208 (81.2%)	218 (82.0%)	0.130	4 (22.2%)	72 (16.2%)	76 (16.5%)	0.503
Group B Streptococcus testing				0.642				0.681				0.845
Negative	2 (100.0%)	85 (69.1%)	87 (69.6%)		7 (70.0%)	157 (61.1%)	164 (61.4%)		12 (66.7%)	305 (68.7%)	317 (68.6%)	
Positive	0 (0.0%)	14 (11.4%)	14 (11.2%)		0 (0.0%)	16 (6.2%)	16 (6.0%)		1 (5.6%)	35 (7.8%)	36 (7.8%)	
Not done	0 (0.0%)	24 (19.5%)	24 (19.2%)		3 (30.0%)	84 (32.7%)	87 (32.6%)		5 (27.8%)	100 (22.5%)	105 (22.7%)	
Perinatal context				0.857				0.545				0.766
Threat of premature labor	1 (50.0%)	59 (47.6%)	60 (47.6%)		4 (40.0%)	64 (24.9%)	68 (25.5%)		5 (27.8%)	97 (21.8%)	102 (22.1%)	
PPROM	0 (0.0%)	25 (20.2%)	25 (19.8%)		0 (0.0%)	45 (17.5%)	45 (16.9%)		5 (27.8%)	135 (30.4%)	140 (30.3%)	
Pre-eclampsia/vascular	0 (0.0%)	13 (10.5%)	13 (10.3%)		4 (40.0%)	72 (28.0%)	76 (28.5%)		7 (38.9%)	132 (29.7%)	139 (30.1%)	
Metrorrhagia	0 (0.0%)	4 (3.2%)	4 (3.2%)		0 (0.0%)	9 (3.5%)	9 (3.4%)		0 (0.0%)	18 (4.1%)	18 (3.9%)	
Chorio amnionitis	1 (50.0%)	21 (16.9%)	22 (17.5%)		2 (20.0%)	52 (20.2%)	54 (20.2%)		0 (0.0%)	16 (3.6%)	16 (3.5%)	
Other	0 (0.0%)	2 (1.6%)	2 (1.6%)		0 (0.0%)	15 (5.8%)	15 (5.6%)		1 (5.6%)	46 (10.4%)	47 (10.2%)	
Delivery route				0.873				0.126				0.581
Vaginal	1 (50.0%)	69 (55.6%)	70 (55.6%)		6 (60.0%)	93 (36.2%)	99 (37.1%)		7 (38.9%)	202 (45.5%)	209 (45.2%)	
Caesarean section	1 (50.0%)	55 (44.4%)	56 (44.4%)		4 (40.0%)	164 (63.8%)	168 (62.9%)		11 (61.1%)	242 (54.5%)	253 (54.8%)	
Perinatal outcomes												
Respiratory distress syndrome	2 (100.0%)	124 (100.0%)	126 (100.0%)	–	10 (100.0%)	240 (93.4%)	250 (93.6%)	0.401	8 (44.4%)	198 (44.6%)	206 (44.6%)	0.990
Surfactant	2 (100.0%)	85 (68.5%)	87 (69.0%)	0.340	5 (50.0%)	59 (23.0%)	64 (24.0%)	0.049	0 (0.0%)	17 (3.8%)	17 (3.7%)	0.398
Bronchopulmonary dysplasia	0 (0.0%)	82 (66.7%)	82 (65.6%)	0.049	3 (30.0%)	52 (20.2%)	55 (20.6%)	0.454	0 (0.0%)	2 (0.5%)	2 (0.4%)	0.775
Intraventicular hemorrhage	1 (50.0%)	51 (41.1%)	52 (41.3%)	0.800	1 (10.0%)	37 (14.4%)	38 (14.2%)	0.696	1 (5.6%)	38 (8.6%)	39 (8.4%)	0.651
Periventricular leukomalacia	0 (0.0%)	4 (3.2%)	4 (3.2%)	0.497	1 (10.0%)	4 (1.6%)	5 (1.9%)	0.142	0 (0.0%)	2 (0.5%)	2 (0.4%)	0.069
Necrotizing enterocolitis	0 (0.0%)	13 (10.5%)	13 (10.3%)	0.629	0 (0.0%)	6 (2.3%)	6 (2.2%)	0.625	0 (0.0%)	5 (1.1%)	5 (1.1%)	0.651
Neonatal infection	0 (0.0%)	40 (32.3%)	40 (31.7%)	0.591	0 (0.0%)	32 (12.5%)	32 (12.0%)	0.312	0 (0.0%)	12 (2.7%)	12 (2.6%)	0.413
Retinopathy	0 (0.0%)	6 (4.8%)	6 (4.8%)	0.909	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Ductus arteriosus	0 (0.0%)	67 (54.0%)	67 (54.0%)	0.122	1 (10.0%)	20 (7.8%)	21 (7.9%)	0.798	2 (11.1%)	5 (1.1%)	7 (1.5%)	<0.001
Death	1 (50.0%)	34 (27.4%)	35 (27.8%)	0.479	2 (20.0%)	13 (5.1%)	15 (5.6%)	0.044	1 (5.6%)	10 (2.3%)	11 (2.4%)	0.367

PPROM, preterm premature rupture of the membranes.
p value < 0.05 was consider statistically significant.

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TABLE 4 Profiles of the mothers and newborns by term during lockdown (from Tuesday 17th of March 2020 to Sunday 10th of May 2020) vs. date to date (from the 17th of March to the 10th of May of years 2017, 2018 and 2019).

	<28 weeks				28–31 ± 6 weeks				32–36 ± 6 weeks			
	Lockdown (*N* = 2)	No lockdown (*N* = 25)	Total (*N* = 27)	*p*-value	Lockdown (*N* = 10)	No lockdown (*N* = 29)	Total (*N* = 39)	*p*-value	Lockdown (*N* = 18)	No lockdown (*N* = 59)	Total (*N* = 77)	*p*-value
Characteristics of mothers and newborns												
Sex				0.957				0.754				0.922
Boy	1 (50%)	13 (52.0%)	14 (51.9%)		6 (60.0%)	19 (65.5%)	25 (64.1%)		10 (55.6%)	32 (54.2%)	42 (54.5%)	
Girl	1 (50%)	12 (48.0%)	13 (48.1%)		4 (40.0%)	10 (34.5%)	14 (35.9%)		8 (44.4%)	27 (45.8%)	35 (45.5%)	
Mother's age	34 (27.00–41.00)	31.80 (21.00–41.00)	31.96 (21.00–41.00)	0.654	33.30 (25.00–41.00)	29.59 (23.00–38.00)	30.54 (23.00–41.00)	0.037	33.35 (24.00–44.00)	32.44 (19.00–43.00)	32.65 (19.00–44.00)	0.566
Premature birth history	0 (0.0%)	2 (8.0%)	2 (7.4.%)	0.678	3 (30.0%)	1 (3.4%)	4 (10.3.%)	0.017	4 (22.2%)	6 (10.1%)	10 (13.0%)	0.203
History of fetal death *in utero*	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	1 (3.4%)	1 (2.6%)	–	0 (0.0%)	1 (1.7%)	1 (1.3%)	0.656
Complete antenatal corticosteroid therapy	2 (100%)	16 (64.0%)	18 (66.7%)	–	6 (60.0%)	20 (69.0%)	26 (66.7%)	0.868	9 (50.0%)	38 (64.4%)	47 (61.0%)	0.441
Magnesium sulfate	1 (50.0%)	18 (72.0%)	19 (70.4%)	0.512	10 (100.0%)	23 (79.3%)	33 (84.6%)	0.118	4 (22.2%)	12 (20.3%)	16 (20.8%)	0.863
Group B Streptococcus testing				0.618				0.419				0.926
Negative	2 (100.0%)	16 (64.0%)	18 (66.7%)		7 (70.0%)	14 (48.3%)	21 (53.8%)		12 (66.7%)	34 (57.6%)	46 (59.8%)	
Positive	0 (0.0%)	4 (16.0%)	4 (16.0%)		0 (0.0%)	2 (6.9%)	2 (5.1%)		1 (5.6%)	4 (6.7%)	5 (6.5%)	
Not done	0 (0.0%)	4 (16.0%)	4 (16.0%)		3 (30.0%)	13 (44.8%)	16 (41.0%)		5 (27.8%)	17 (28.8%)	22 (28.6%)	
Perinatal context				–				0.588				0.184
Threat of premature labor	1 (50.0%)	13 (52.0%)	14 (51.9%)		4 (40.0%)	10 (34.5%)	14 (35.9%)		5 (27.8%)	4 (6.8%)	9 (11.7%)	
PPROM	0 (0.0%)	1 (4.0%)	1 (3.7%)		0 (0.0%)	4 (13.8%)	4 (10.3%)		5 (27.8%)	24 (40.7%)	29 (37.7%)	
Pre-eclampsia/vascular	0 (0.0%)	2 (8.0%)	2 (7.4%)		4 (40.0%)	8 (27.6%)	12 (30.8%)		7 (38.9%)	21 (35.6%)	28 (36.4%)	
Metrorrhagia	0 (0.0%)	1 (4.0%)	1 (3.7%)		0 (0.0%)	3 (10.3%)	3 (7.7%)		0 (0.0%)	2 (3.4%)	2 (2.6%)	
Chorio amnionitis	1 (50.0%)	8 (32.0%)	9 (33.3%)		2 (20.0%)	3 (10.3%)	5 (12.8%)		0 (0.0%)	3 (5.1%)	3 (3.9%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (3.4%)	1 (2.6%)		1 (5.6%)	5 (8.5%)	6 (7.8%)	
Delivery route				0.869				0.065				0.994
Vaginal	1 (50.0%)	14 (56.0%)	15 (55.6%)		6 (60.0%)	8 (27.6%)	14 (35.9%)		7 (38.9%)	23 (39.0%)	30 (39.0%)	
Caesarean section	1 (50.0%)	11 (44.0%)	12 (44.4%)		4 (40.0%)	21 (72.4%)	25 (64.1%)		11 (61.1%)	36 (61.0%)	47 (61.0%)	
Perinatal outcomes												
Respiratory distress syndrome	2 (100.0%)	25 (100.0%)	27 (100.0%)	–	10 (100.0%)	27 (93.1%)	37 (94.9%)	0.394	8 (44.4%)	23 (39.0%)	31 (40.3%)	0.679
Surfactant	2 (100.0%)	17 (68.0%)	19 (70.4%)	0.340	5 (50.0%)	8 (27.6%)	13 (33.3%)	0.195	0 (0.0%)	1 (1.7%)	1 (1.3%)	0.578
Bronchopulmonary dysplasia	0 (0.0%)	16 (64.0%)	16 (59.3%)	0.076	3 (30.0%)	5 (17.2%)	8 (20.5%)	0.968	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Intraventicular hemorrhage	1 (50.0%)	10 (40.0%)	11 (40.7%)	0.782	1 (10.0%)	5 (17.2%)	6 (15.4%)	0.584	1 (5.6%)	5 (8.5%)	6 (7.8%)	0.686
Periventricular leukomalacia	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	1 (10.0%)	1 (3.4%)	2 (5.1%)	0.331	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Necrotizing enterocolitis	0 (0.0%)	3 (12.0%)	3 (11.1%)	0.603	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Neonatal infection	0 (0.0%)	10 (40.0%)	10 (37.0%)	0.501	0 (0.0%)	2 (6.9%)	2 (5.1%)	0.395	0 (0.0%)	1 (1.7%)	1 (1.3%)	0.576
Retinopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Ductus arteriosus	0 (0.0%)	14 (56.0%)	14 (51.9%)	0.127	1 (10.0%)	1 (3.4%)	2 (5.1%)	0.418	2 (11.1%)	1 (1.7%)	3 (3.9%)	0.071
Death	1 (50.0%)	8 (32.0%	9 (33.3%)	0.603	2 (20.0%)	1 (3.4%)	3 (7.7%)	0.090	1 (5.6%)	0 (0.0%)	1 (1.3%)	0.068

PPROM, preterm premature rupture of the membranes.
p value < 0.05 was consider statistically significant.

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reduction in preterm birth during pandemic compared with pre pandemic period, but further subgroup analysis showed that there were no difference in studies from multicenter or low and middle income countries (24). According to these studies the potential positive effects of lockdown on prematurity and low birth weight were due to several factors. These included the decrease in social interaction, the shutdown of schools, the waring of masks and an increase in hygiene, which may have decreased the risk of contact with pathogens and thus a decrease in maternal infection (15–21).

There are many factors of risk of prematurity but the ethology is sometimes not well understood. They can be maternal, obstetric, infectious or environmental. The factors of risk of prematurity that may have changed during lockdown include atmospheric pollution (due to limited journeys), rest and maternal stress (with more time at home, the set up of work from home, more family support with the partner at home and certain financial assistance from governments). However, these factors of risk remain debatable and have yet to be proven. Atmospheric pollution, which may have decreased during lockdown, is a controversial factor of risk since it depends on the type of particule studied and the trimester of exposure (25, 26). With respect to rest, a systematic review by Cochrane (27) published in 2015, did not find evidence to show that bedrest reduced prematurity, on the contrary it may have negative effects such as an increase in demineralisation of bone and deconditioning during exercise or an increased risk of deep vein thrombosis (28). With respect to maternal stress, this is a subjective element with different definitions according to the studies so it is difficult to establish an association with perinatal issues such as prematurity. While it is qualified as a risk factor some studies do not report any difference and even report a decrease in prematurity (29). There also exists a hypothesis suggesting that stressful events do not have the same impact when experienced in the first, second or third trimester of pregnancy, with a higher degree of stress at the beginning of pregnancy (30).

It should be noted that preventive measures exist to reduce prematurity (31, 32). There are three types: primary prevention that concerns all women, secondary prevention to reduce and eliminate already existing risks and tertiary prevention to improve the outcome of infants born prematurely. Tertiary prevention has been the most developed in recent years, with the set up of networks of organisations providing perinatal care and health care to mothers and their newborns in adapted maternities, of antenatal corticosteroid therapy use and administration of magnesium sulphate.

5. Conclusion

The objective of our study was to examine the consequences of lockdown in France due to the SARS-CoV-2 pandemic on prematurity before 37 weeks of gestation in the level III maternity of the Nice University Hospital. We did not find evidence of an association between lockdown and prematurity, which is in agreement with published meta-analyses. Certain factors of risk such as atmospheric pollution, rest and maternal stress that were discussed during lockdown are debatable and their involvement remains to be demonstrated. The identification of the factors of risk of prematurity and the preventive measures are still a major public health issue.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ML, KL, and BF-G: have made a substantial contribution to the concept of the article and acquisition of date for the article KL: have made a substantial contribution to the interpretation and analysis of data for the article MM, SE, AH-B, and IG-R: revised the article for the important intellectual content and approved the version to be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Covid-19 omicron variant infection in neonates of Guangdong province-a report of 52 cases

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Objective: To analyze the clinical characteristics of neonatal infection during the outbreak of COVID-19 omicron variant in Guangdong province of China.
Method: The clinical data of neonates infected with COVID-19 omicron variant were collected from three hospitals of Guangdong province, their epidemiological history, clinical manifestation and prognosis were summarized.
Results: From December 12, 2022 to January 15, 2023, a total of 52 neonates with COVID-19 infection were identified across three hospitals in Guangdong Province, including 34 males and 18 females. The age of diagnosis was 18.42 ± 6.32 days. 24 cases had clear contact history with adults who were suspected to be infected with COVID-19. The most common clinical manifestation was fever (43/52, 82.7%), the duration of fever was 1–8 days. The other clinical manifestations were cough (27/52, 51.9%), rales (21/52, 40.4%), nasal congestion (10/52, 19.2%), shortness of breath (2/52, 3.8%), and vomiting (4/52, 7.7%). C-reactive protein was only increased in 3 cases. Chest radiological examination was performed in 42 neonates, twenty-three cases showed abnormal chest radiographic findings, including ground-glass opacity and consolidation. Fifty cases were admitted with COVID-19 presentation, two cases were admitted for jaundice. The hospital stay was 6.59 ± 2.77 days. The clinical classification included 3 cases of severe COVID-19 and one critical case. Fifty-one cases were cured and discharged after general treatment, and one critical case with respiratory failure was intubated and transferred to another hospital.
Conclusion: The COVID-19 omicron variant infection in neonates is usually mild. The clinical manifestation and laboratory results are not specific, and the short-term prognosis is good.

KEYWORDS

COVID-19, omicron, neonate, China, prognosis, SARS-CoV-2

1. Introduction

COVID-19 is an acute respiratory infectious disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), neonates are also susceptible populations for COVID-19 infection (1–4). China underwent a surge of omicron infections after abandoning "zero COVID" strategies on December 7, 2022 (5). Massive children infections including neonates are speculated. According to the report of the Chinese Center for Disease Control and Prevention (CDC), the epidemic strains are mainly omicron BA.5.2 and BF.7 (6). From December 8, 2022 to January 2023, an epidemic of omicron strain also occurred in Guangdong province. There was no report of omicron variant infection in neonates from China after this epidemic. Confirmed neonatal SARS-CoV-2 infection was uncommon over the past 3 years of the pandemic in China. Infection trend in the neonates broadly followed that seen in the general population, although at a lower level. Since the literature of the disease presentation and outcome in neonates is sparse, there is an urgent need to understand the clinical characteristics and management of neonates with community acquired COVID-19.

Here, we summarize the early clinical characteristics of COVID-19 infection in neonates identified during this outbreak in three hospitals of Guangdong province, and analyze the epidemiological history, treatment measures and prognosis of the infection, and provide reference experience for the prevention and treatment of neonatal COVID-19 omicron variant infection.

2. Methods

2.1. Study population

From December 8, 2022 to January 15, 2023, neonates admitted in Neonatal wards of People's Hospital of Yangjiang (Tertiary hospital, the biggest hospital in Yangjiang area), Chaozhou Central Hospital (Tertiary hospital with the biggest Neonate ward in Chaozhou area) and Pengpai Memorial Hospital (Secondary hospital in Shanwei area) were retrospectively reviewed. The diagnostic criteria for neonates with COVID-19 were: (1) age ≤28 days old; (2) positive for SARS-CoV-2 nucleic acid in nasal swab and (or) oropharynx swab, the presence of SARS-CoV-2 viral RNA was tested using an in-house Taqman rt-real-time PCR assay targeting N and ORF1ab genes. The date of disease onset was defined as the day a symptom was noticed. Fever was defined as a temporary increase in the body's temperature (over 37.2°C). Neonatal anemia was defined as a neonate had a lower hemoglobin (lower than 130 g/dl). Demographic and clinical records, and laboratory results were reviewed and collected by the ordering pediatricians from electronic medical records. Information recorded included date of birth, sex, weight at birth, mode of delivery, gestational age, feeding mode, Apgar score, signs, laboratory findings, medical records and underlying comorbidities. Laboratory tests including blood routine, renal and hepatic function test were also reviewed. Epidemiological history, chest imaging findings and outcomes were also collected.

This study was approved by the Ethics Committee of People's Hospital of Yangjiang (20230003), Ethics Committee of Pengpai Memorial Hospital and Chaozhou Central Hospital. As the patient's data were analyzed anonymously, a waiver of written consent was approved by the Ethics Committee of the three Hospitals.

2.2. Clinical diagnosis and classification

COVID-19 diagnosis and classification criteria were based on "New coronavirus pneumonia diagnosis and treatment protocol (trial version 10)", which was issued by the national health commission of P. R. China (7). Mild infection was defined as having only mild clinical manifestations such as fever and cough but no imaging manifestations of pneumonia; the moderate type was defined as those with clinical manifestations and imaging manifestations of pneumonia; severe type was defined as persistent fever for more than 3 days, shortness of breath, hypoxemia, dyspnea, lethargy, convulsion, difficulty in feeding or refusing to eat, and obvious imaging manifestations of pneumonia; critical type was defined as respiratory failure requiring respiratory support, shock, or other systemic organ failure.

2.3. Discharge criteria

The clinical condition was stable and the symptoms and signs disappeared.

2.4. Statistical analysis

SPSS 19.0 software was used for statistical analysis. Categorical variables were reported as number and percentage, while continuous variables were shown as median and interquartile ranges (laboratory results) or as mean and standard deviation (SD).

3. Results

3.1. Demographics

From December 12, 2022 to January 15, 2023, fifty-two neonates with COVID-19 were admitted in the Neonatal wards of People's Hospital of Yangjiang ($n = 18$), Pengpai Memorial Hospital ($n = 8$), and Chaozhou Central Hospital ($n = 26$) of Guangdong province of China (**Figure 1**). They were positive for SARS-CoV-2 polymerase chain reaction (PCR) test, including 34 males and 18 females; their gestational age was 36–41 weeks and birth weight was 3.24 ± 0.316 kg; thirty cases were vaginal delivery and twenty-two cases were cesarean section; seven cases were exclusively breast feeding, thirteen cases were exclusively

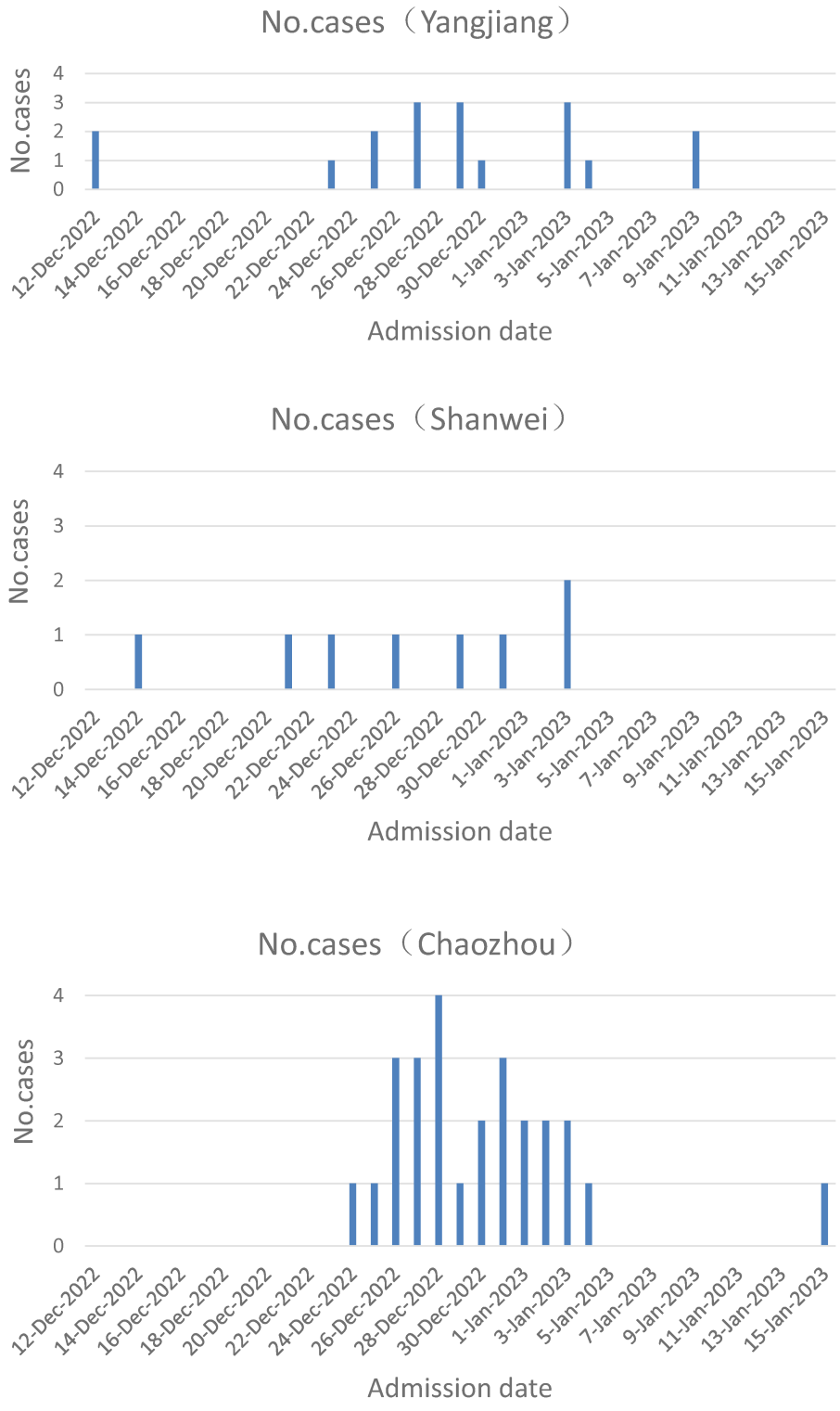

FIGURE 1
Case numbers of three hospitals at admission date.

formula feeding, twenty-seven cases were mixed feeding and feeding pattern was unknown in 5 cases. Median age at admission was 19 days for all neonates (Table 1). Twenty-four cases had clear contact history with adults who were suspected to be infected with SARS-CoV-2 after birth.

3.2. Clinical characteristics

Upon admission, the most common clinical manifestation was fever ($n = 43$; 82.7%) among the 52 cases. During the course of the disease, the duration of fever was 1–8 days, the peak temperature

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TABLE 1 General information and clinical features of 52 newborns with omicron variant of COVID-19.

Variables	Values
Age, days at admission ($n = 52$)	
Mean ± SD	18.42 ± 6.32
Median (IQR)	19 (11–22)
≤7	2 (3.85%)
8–14	15 (28.85%)
15–21	17 (32.7%)
22–28	18 (34.62%)
Sex ($n = 52$)	
Female	18 (34.6%)
Male	34 (65.4%)
Mode of delivery ($n = 52$)	
Cesarean delivery	22 (42.3%)
Vaginal delivery	30 (57.7%)
Birthweight (kg) ($n = 52$)	
Mean ± SD	3.24 ± 0.316
Presenting features[a] ($n = 52$)	
Fever	43 (82.7%)
Cough	27 (51.9%)
Shortness of breath or difficulty breathing	2 (3.8%)
Nasal congestion	10 (19.2%)
Vomiting	4 (7.7%)
Poor appetite	9 (17.3%)
Diarrhoea	2 (3.8%)
Seizure	1 (1.9%)
Rales	21 (40.4%)
Gestational age (weeks) ($n = 52$)	
Mean ± SD	38.67 ± 1.37
Median(IQR)	39 (38–40)
Duration of fever days ($n = 42$)	
Mean ± SD	2.52 ± 1.27
Median(IQR)	2 (2–3)
Peak temperature	
≥39°C	4 (9.5%)
<39°C	38 (90.5%)
Comorbidities[b] ($n = 52$)	
None	24 (46.2%)
Jaundice	11 (21.2%)
Anemia	22 (42.3%)
Urinary tract infection	2 (3.8%)
Hyponatremia	2 (3.8%)
Hyperglycemia	1 (1.9%)
Gastrointestinal disorders	5 (9.6%)
Pertussis	1 (1.9%)
Encephalitis	1 (1.9%)
Convulsions	1 (1.9%)
Feeding pattern ($n = 52$)	
Breast feeding	7 (13.5%)
Formula feeding	13 (25%)
Mixed feeding	27 (51.9%)
Unknown	5 (9.6%)
Length of hospital stay, days ($n = 52$)	
Mean ± SD	6.59 ± 2.77
Median (IQR)	5 (4–6)
Range	10 h–17 d
Highest category of oxygen supplementation ($n = 52$)	
None	50 (96.2%)
Nasal prong oxygen	2 (3.8%)
Mechanical ventilation	1 (1.92%)
Antibiotic (n=52)	17 (32.7%)
Disease severity (n=52)	
Asymptomatic[c]	2 (3.8%)
Mild	24 (46.2%)
Moderate	22 (42.3%)
Severe	3 (5.77%)
Critical	1 (1.92%)
Outcomes ($n = 52$)	
Cured	51 (98.1%)
Transfer to another hospital	1 (1.9%)

Data are n (%), mean (SD), range, or median (IQR), unless otherwise stated.
[a]Multiple presenting features were possible.
[b]Multiple Comorbidities were possible.
[c]2 cases were admitted for jaundice, absent for syndromes of COVID-19 such as fever and cough.

was 37.4°C–40.1°C, and it was over 39°C in 4 cases. Fever was the only presentation in 14 cases. The respiratory symptoms were cough ($n = 27$, 51.9%), nasal congestion ($n = 10$, 19.2%), shortness of breath ($n = 2$, 3.8%). Lung rales could be identified in 21 cases upon auscultation. Twelve cases had digestive symptoms, including anorexia ($n = 9$, 17.3%), vomiting ($n = 4$, 7.7%), and diarrhea ($n = 2$, 3.8%). One case had fever (37.8°C) and cough for one day and was admitted in one hospital, she was treated for 4 days and discharged with normal temperature, one day later, she had fever (37.7°C) again, then she was admitted and treated for 3 days, and released without fever.

Among infants with COVID-19, thirty-two cases had at least 1 comorbidity, the most prevalent was anemia (22, 42.3%), jaundice accounted for 21.2% (11/52) of comorbidities. Gastrointestinal disorders was observed in 5 cases, and 2 cases of urinary tract infection, two cases of hyponatremia, one case of hyperglycemia, one case of pertussis and one critical case with suspected encephalitis were also identified.

One critical case of 28 days old boy was admitted for cough and respiratory distress, he had no fever, presented with persistent seizure, and his condition deteriorated rapidly, he was diagnosed as respiratory failure, encephalitis, and hyponatremia. He was intubated and received mechanical ventilation, then was transferred to another hospital for further therapy.

3.3. Laboratory test and chest imaging

Complete blood cell count, blood biochemistry and infection biomarkers were tested upon admission. Laboratory tests revealed leukopenia ($n = 22$, 42.3%), neutropenia ($n = 10$, 19.2%), monocytosis ($n = 52$, 100%). Lymphopenia only occurred in 3 cases. Hemoglobin was decreased in 22 cases (anemia). ALT

increased in one case, and AST increased in 20 cases, they were within 2 times of upper reference limits, implied no severe liver injury in this study group. C-reactive protein (CRP) was elevated in only 3 neonates. IL-6 was slightly increased in 2 of 8 tested cases in one hospital (People's Hospital of Yangjiang) (**Table 2**).

Twenty cases were also tested for another 7 common respiratory viruses (influenza virus A and B, parainfluenza virus 1, 2, and 3, respiratory syncytial virus, and adenovirus) by immunofluorescence assay, they were negative for these viruses.

TABLE 2 Laboratory results and radiological findings.

Variables	Values	Normal values
Hemoglobin, g/dl ($n = 52$), Mean ± SD	137.17 ± 21.49	130–175 g/L
median (IQR)	135 (126–146)	
<130 g/L, *n* (%)	22 (42.3%)	
Platelets, $\times 10^9$/L ($n = 52$), Mean ± SD	344.60 ± 97.07	125–350 × 10^9 cells/L
Median (IQR)	347 (278–413)	
WBC count, $\times 10^9$/L ($n = 52$), Mean ± SD	9.00 ± 3.11	3.5–9.5 × 10^9 cells/L
Median (IQR)	9.81 (7.93–10.89)	
>9.5 × 10^9/L, *n* (%)	22 (42.3%)	
Neutrophil count, $\times 10^9$/L($n = 52$), Mean ± SD	3.07 ± 1.66	1.8–6.3 × 10^9 cells/L
median (IQR)	2.41 (1.9–3.79)	
Lymphocyte count, $\times 10^9$/L ($n = 52$), Mean ± SD	3.82 ± 2.43	1.1–3.2 × 10^9 cells/L
median (IQR)	4 (2.41–6.35)	
<1 × 10^9/L, *n* (%)	3 (5.8%)	
Monocyte count, $\times 10^9$/L ($n = 52$), Mean ± SD	1.76 ± 0.77	0.1–0.6 × 10^9 cells/L
median (IQR)	1.53 (1.01–2.67)	
>0.6 × 10^9/L, *n* (%)	52 (100%)	
C-reactive protein, mg/L ($n = 52$), Mean ± SD	2.70 ± 4.89	0–6 mg/L
median (IQR)	1.84 (1.2–3.21)	
>6 mg/L, *n* (%)	3 (5.8%)	
IL-6, pg/ml ($n = 8$), Range	0.49–57.19	0–5.3 pg/ml
>5.3 pg/ml	2 (25%)	
ALT, U/L ($n = 51$), Mean ± SD	21.03 ± 10.25	9–50 U/L
median (IQR)	15.4 (12–22.4)	
>50 U/L, *n* (%)	1 (1.9%)	
AST, U/L ($n = 52$), Mean ± SD	41.94 ± 22.31	15–40 U/L
median (IQR)	36.4 (30–56.4)	
>40 U/L, *n* (%)	20 (38.5%)	
LDH, U/L ($n = 52$), Mean ± SD	393.21 ± 152.61	109–450 U/L
median (IQR)	362 (339–458)	
>450 U/L, *n* (%)	4 (7.7%)	
CK, U/L ($n = 52$), Mean ± SD	152.65 ± 120.24	50–310 U/L
median (IQR)	112 (74–182)	
>310 U/L, *n* (%)	2 (3.8%)	
CK-MB, U/L ($n = 52$), Mean ± SD	25.27 ± 14.69	0–24 U/L
median (IQR)	31.8 (26.7–38.2)	
>24 U/L, *n* (%)	24 (46.2%)	
Positive chest CT finding ($n = 21$), *n* (%)	18 (85.7%)	negative
Positive chest x-ray finding ($n = 21$), *n* (%)	5 (23.8%)	negative

WBC, White blood cells; ALT, Alanine aminotransferase; AST, Aspartate transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, Creatine Kinase Myocardial Band; CRP, C-reactive protein.

Blood bacteria culture was performed in 11 cases, and *hemolytic staphylococcus* was identified in one case. Respiratory specimen culture was performed in 6 cases, five cases were identified with infection of *staphylococcus aureus*.

Chest x-rays were performed in 21 infants (People's Hospital of Yangjiang and Pengpai Memorial Hospital) and pneumonia was detected in 5 of them (23.8%). Chest computed tomography (CT) was performed in 21 neonates (Chaozhou Central Hospital), abnormal chest radiographic findings, including ground-glass opacity and consolidation, were identified in 18 cases.

3.4. Clinical classification

COVID-19 disease was deemed by clinicians to be the primary diagnosis in 50 (96.15%) of 52 infants, while in 2 jaundiced infants (3.85%) it was an incidental diagnosis. Based on their clinical presentations, twenty-four cases were mild, twenty-two cases were moderate for their radiological chest findings, three cases met the criteria for severe COVID-19 infection and one critical case were diagnosed according to the classification of China CDC (6), and no child was diagnosed with multi-system inflammatory syndrome in children (MIS-C), as per USA case definition (8) (**Table 1**).

3.5. Treatment and prognosis

None of the 52 neonates received any antiviral drug therapy or specific therapy for SARS-CoV-2. Seventeen cases were treated with antibiotics at the beginning of the disease and terminated after bacterial infection was excluded or cured. The duration of antibiotics use was 1–5 days. Two cases presented with mild respiratory distress and need nasal oxygen inhalation, and one critical case was intubated and need mechanical ventilation. The symptoms of 51 neonates including 3 severe cases relieved after general treatment. One critical case was transferred to another hospital. The duration of hospitalization was 10 h–17 days. During hospitalization, mothers were separated from their infants, and breastfeeding was discontinued.

4. Discussion

Since the first half of 2022, the omicron variant was the most prevalent strain of COVID-19 in China mainland, which was characterized by its stronger infectivity and mild clinical symptoms than other strains (9, 10). China underwent a surge of omicron infections after abandoning "zero COVID" strategies on December 7, 2022 (5). Subsequently, the SARS-CoV-2 Omicron variant has quickly spread throughout China, affecting individuals of all ages. This report outlines our experience with neonates diagnosed with COVID-19 in three hospitals across Guangdong Province during the SARS-CoV-2 Omicron epidemic.

The main symptom of newborns with omicron variant infection was fever in our study cohort, and the other symptoms

mainly involved respiratory and digestive system, which were similar to the clinical manifestations of other strains of neonatal infection (11). It is suggested that routine detection of SARS-CoV-2 nucleic acid may be necessary for febrile neonates during the epidemic period of omicron variant of COVID-19 (11). In addition, digestive system symptoms in this study were less, no other systems such as skin and circulatory system symptom was identified. It is suggested that the clinical manifestation of omicron strain may be different from that of other strains (12), this needs to be confirmed by a larger sample size.

A review described SARS-CoV-2 infection in neonates, totally 58 neonates were summarized with SARS-CoV-2 infection (4 cases were a congenital infection), and 29 (50%) were symptomatic (23 required ICU), respiratory symptoms was the predominant manifestation (70%) (11). No mortality was reported in SARS-CoV-2-positive neonates (11). All 52 cases in our study were symptomatic, because asymptomatic infants need not to come to see doctors. The risk of SARS-CoV-2 infection in neonates is extremely low (13, 14), one reason is that the neonates have SARS-CoV-2 antibody through vaccination of his/her mother, the other reason is the strong measures (including separation of baby and COVID-19 mother) taken to prevent perinatal period infection among high-risk groups in China (14). In our study, mothers were separated from their in-hospital infants, and breastfeeding was discontinued. There have been varying guidelines regarding the separation of mothers with COVID-19 from their infants and breastfeeding during hospitalization. Initially, some hospitals (including our hospital) recommended separating mothers with COVID-19 from their infants as a precautionary measure to prevent the transmission of the virus. However, recent evidence suggests that the risk of transmission from a mother with COVID-19 to her infant through breastfeeding is low. If appropriate measures are applied, it is not necessary to separate the neonates from his/her mother, and breast feeding is encouraged (15).

Our study neonates were 3–28 days old, nearly half of them (24/52) could trace their infection routes from their surroundings. No congenital infection was identified in our study cohort. Twenty-four neonates from SARS-CoV-2 RNA positive mothers were not infected from their mothers in the same period of one hospital (data not shown). Based on the available literature and our data, we presume that SARS-CoV-2 vertical transmission, including transplacental route, is rare, and exposed neonates generally show favorable health outcomes (16).

Lymphopenia was consistently identified in adults, and it was associated with increased disease severity of COVID-19 (17). Only 3 of 52 neonates experienced lymphopenia in our study, the absence of lymphopenia observed in neonates with COVID-19 may be due to their relatively high thymic output during this developmental stage. Additionally, the immature state of their monocytes may result in a reduced cytokine response, which is indicative of a more favorable immune system response to SARS-CoV-2. Our study further supports this by showing that neonates with COVID-19 had lower levels of IL-6. As a result, there is a reduced risk of excessive inflammation associated with severe lung injury (18, 19). Monocytosis was detected in all 52 neonates, increased monocytes may represent a physiological and immature response of the marrow of infants to a variety of exogenous stimuli including COVID-19 (20).

All 52 cases were symptomatic in this group of newborns, 3 cases were severe and one was critical. Previous reports have indicated that neonatal SARS-CoV-2 infection can result in both common and severe cases, with reported cases of mortality (15). This study is consistent with previous studies, that adults and children showed mild clinical symptoms of omicron variant infection than other counterparts (8). Most of the severe or critical cases of neonates reported in the past were complicated with premature birth, congenital malformation or other underling diseases (11, 21), while all of the severe or critical cases in our group were healthy in the past.

The treatment protocol of neonatal COVID-19 infection is mainly appropriate nursing, and anti-virus drug is not recommended (22). Fifty-one neonates in this group recovered after close monitoring and general treatment, and they presented a self-limited course of disease, and the short-term prognosis was good, but the number of breast-feeding cases was significantly lower than that before admission, which may be related to the separation of mothers and infants and the influence of mother's anxiety on lactation during the epidemic period. Reports suggest that neonatal COVID-19 could have implications for brain development, highlighting the importance of long-term follow-up and prognosis monitoring (23).

Twenty-one cases of infants received chest x-ray, and only 5 cases were identified with pneumonia; while 21 cases of infants received chest CT test, eighteen cases was complicated with pneumonia. It seemed that CT could detect more abnormal findings than that of x-ray, this is consistent to previous study from Turkey (18). However, these additional CT findings did not affect medical management. Therefore, CT is not clinically indicated for the initial evaluation of mild to moderately symptomatic infants with COVID-19 pneumonia (24). As for severe and critical cases, CT could provide detailed information for clinical decision (24).

There are several limitations to our study that must be acknowledged. First, our study only includes neonates who sought medical attention and exhibited symptoms of respiratory system and fever, and therefore does not include asymptomatic neonates or atypical cases. As a result, our case cohort may be biased towards more severe illness. Additionally, the two hospitals included in our study are tertiary hospitals, which may represent a relatively higher severity of COVID-19 cases in neonates and may not reflect the overall distribution of disease severity in neonates. Although all of the neonates were treated according to the proposal provided by the national health commission of P. R. China (7), treatment measures and follow-up among three hospitals are not identical, and designing a strict protocol would be impossible and unethical. Furthermore, most of the infants do not have a respiratory PCR panel to assess co-infection, we could not exclude the possibility of co-infection in all cases.

In summary, the Covid-19 omicron variant infection in neonates is usually mild. Some infants presented with mild

symptoms but were hospitalized due to their very young age. The clinical manifestation and laboratory results are not specific, and the short-term prognosis is relatively good.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of People's Hospital of Yangjiang, Ethics Committee of Pengpai Memorial Hospital and Chaozhou Central Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

LY conceived and designed the study and wrote manuscript. CL, JL, YM, XW, BX, SH, YX, and YC performed the clinical practices and collected the data. YY and FL analyzed the data and wrote the manuscript. LL, YL, GZ, YH and YC collected and analyzed the data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Increased newborn NICU admission for evaluation of hypoxic-ischemic encephalopathy during COVID-19 pandemic in a public hospital

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Background: Prenatal and perinatal care of pregnant mothers has been adversely affected during the COVID-19 pandemic. Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal death and long-term neurological disabilities. Therapeutic hypothermia is effective for neonatal HIE. This study evaluated the effect of the pandemic on neonatal HIE.

Methods: This retrospective single-center study compared neonatal HIE evaluation and hypothermia treatment between pre-COVID-19 pandemic (1 January 2018–31 December 2019) and COVID-19 pandemic (1 January 2020–31 December 2021) periods. Infants with abnormal neurological examination and or significant metabolic acidosis were admitted to NICU for evaluation of HIE and therapeutic hypothermia. Demographics, NICU admission and interventions, and neonatal outcomes were compared between infants born during the two periods using χ^2, *t*-test, and Wilcoxon rank-sum test as appropriate. Statistical Process Control charts show the yearly proportion of infants evaluated for HIE and those treated with therapeutic hypothermia.

Results: From the pre-pandemic to the pandemic period, the proportion of infants that met HIE screening criteria increased from 13% to 16% ($p < 0.0001$), the proportion of infants admitted to NICU for HIE evaluation increased from 1% to 1.4% ($p = 0.02$), and the maternal hypertension rates of the admitted infants increased from 30% to 55% ($p = 0.006$). There was no difference in the proportions of the infants diagnosed with HIE (0.7% vs. 0.9%, $p = 0.3$) or treated with therapeutic hypothermia (0.2% vs. 0.3%, $p = 0.3$) between the two periods. There were no differences in the HIE severity and outcomes of the infants treated with therapeutic hypothermia between the two periods.

Conclusion: During the COVID-19 pandemic, we observed a significant increase in NICU admission for HIE evaluation. While we did not find significant increases in neonatal HIE and the need for therapeutic hypothermia, larger studies are needed for a comprehensive assessment of the impact of the COVID-19 pandemic on neonatal HIE.

KEYWORDS

COVID-19 pandemic, HIE (hypoxic ischaemic encephalopathy), therapeutic hypothermia, metabolic acidosis, maternal hypertension

Introduction

Neonatal encephalopathy is a leading cause of infant mortality and long-term neurodevelopmental abnormalities (1–4). It is a clinically defined syndrome of newborns manifested by an abnormal level of consciousness or seizures, often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes (5). Hypoxic-ischemic encephalopathy (HIE) is the subset of neonatal encephalopathy with evidence of a recent hypoxic–ischemic cause of the encephalopathy. Therapeutic hypothermia (TH), initiated within the first 6 h of life, is the only proven effective neuroprotective therapy for moderate and severe neonatal HIE (6–10). Timely evaluation of newborns at risk of HIE and early initiation of TH is critical for better outcomes (11, 12).

The COVID-19 pandemic has had a profound impact on prenatal and perinatal care. While COVID-19 infection during pregnancy directly increases maternal and neonatal morbidity and mortality (13–16), the indirect factors associated with the pandemic also adversely affect maternal health, pregnancy, and neonatal outcomes (17). During the COVID-19 pandemic, many aspects of the healthcare system were disrupted, and pregnant women experienced fear, mental stress, and a worsening in socioeconomic disparities (17, 18). Many studies have shown increased pregnancy complications, including maternal diabetes, hypertension, and obesity during the pandemic (19–26). These complications are known risk factors for perinatal sentinel events and fetal and neonatal hypoxic-ischemic injury (27–30).

To date, there is limited information on the effect of the COVID-19 pandemic on neonatal HIE. Our institution established standardized protocols for HIE screening, evaluation, and TH in 2008. This study compared our HIE data between the pre-COVID-19 and COVID-19 periods to assess the effect of the pandemic on the incidence and outcomes of neonatal HIE.

Methods

Study design and subjects

This is a single-center, retrospective, observational study conducted in a public safety-net hospital. The study includes two time periods: the pre-COVID-19 period (January 2018–December 2019) and the COVID-19 period (January 2020–December 2021). We included infants born at ≥35 weeks gestation during the study periods. Infants with no intent to resuscitate or those who died in the delivery room were excluded. The study was approved by the institutional review board.

Standardized protocols for HIE screening, evaluation and therapeutic hypothermia in infant ≥35weeks GA

Our standardized neonatal HIE evaluation and total body TH protocols were established in 2008 based on the published multicenter randomized controlled trials (6, 7), which have not been changed since then. Cord blood gas (CBG) with pH <7.15 and/or base deficit (BD) >10 mmol/L are reported to NICU immediately. The HIE screening and evaluation process is shown in **Figure 1**. HIE screening criteria includes a history of perinatal sentinel hypoxic or ischemic events, DR resuscitation with chest compressions or positive pressure ventilation ≥10 min, 5 min Apgar scores ≤5, abnormal neurological examination at birth, and/or CBG with pH <7.15 and/or BD > 10 mmol/L. Infants who meet the screening criteria are examined by pediatric providers. Infants with abnormal neurological examination and or CBG pH <7.0 and/or BD > 16 mmol/L are admitted to NICU for HIE evaluation and treatment. Infants who have normal neurological examination at birth, but with persistent metabolic acidosis >10 mmol/L or if neurological examination becomes abnormal during re-evaluation at one hour of life are admitted to NICU. Infants who meet criteria for TH (**Figure 1**) are cooled as soon as possible. Infants with an abnormal neurological examination but do not meet the TH criteria on initial assessment continue to be monitored and evaluated for up to five hours of life. Ongoing evaluation includes follow-up infant blood gas within the first hour of life, serial neurological examinations, bedside two-channel (C3-P3, C4-P4) aEEG monitoring (Natus Medical, Middleton, WI, USA), and laboratory tests for assessing multiorgan injuries (29, 31). Hypothermia is initiated in infants with persistent or worsening neurological examination, abnormal aEEG (with raw EEG tracing) and/or evidence of multiorgan injuries. HIE evaluation ends if the neurological examination is normalized during the first hours of life.

Total body TH is performed according to the published method (6). During TH, infants' neurological status is assessed by daily neurological examination, continuous bedside aEEG/EEG, and cerebral O2 saturation monitoring. These infants are evaluated and followed by pediatric neurology service, including full channel video EEG evaluation. Brain MRI is performed after TH is completed and when the infant is medically stable to assess brain injury, generally on day of life 4–7. Brain MRI is reviewed by a pediatric radiologist or a neuroradiologist. The severity of brain injury is scored using the scoring system published by Barkovich et al. (32).

Data collection

Maternal and infant demographics, maternal hypertension (chronic hypertension in pregnancy, and gestational hypertension and preeclampsia) (33, 34), diabetes (pre-gestational and gestational) (35, 36), infection, perinatal events, DR interventions, HIE screening, NICU admission for HIE evaluation, TH, and length of NICU stay were obtained from NICU database and electronic medical records.

Demographics, DR measures, NICU interventions, and neonatal outcomes were compared between infants admitted to NICU for HIE evaluation during pre-pandemic and pandemic periods using χ^2, Fisher's exact, *t*-test, Wilcoxon (Mann–Whitney) rank-sum test as appropriate. STATA 14.0 (Statacorp, TX, USA) was used for statistical analysis. A p-value <0.05 was considered significant. We used Statistical Process Control (QI macros 2019 Excel add-on software, KnowWare International, Denver, CO, USA) to show the yearly proportion of infants evaluated for HIE in NICU and infants treated with TH as p charts.

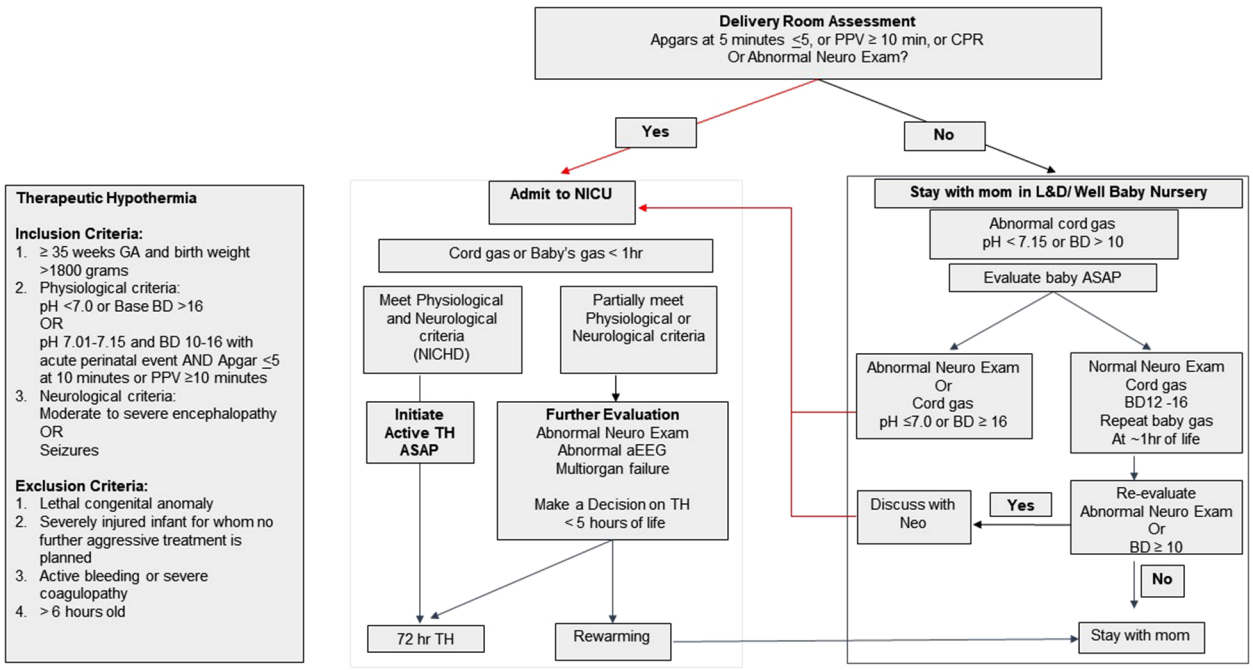

FIGURE 1
Hypoxic ischemic encephalopathy (HIE) screening and evaluation flow chart and criteria for initiating therapeutic hypothermia (TH).

Results

During the four-year study period, there were 10,956 infants born at GA of ≥35 weeks (pre-COVID-19, $n = 5{,}638$, COVID-19, $n = 5{,}318$) (Table 1) at our institution. Of these deliveries, 3,910 CBG were done, and there was no difference in the percentages of CBG between the two periods (35% vs. 36%, $p = 0.7$). From the pre-COVID-19 period to the COVID-19 period, the proportion of infants that met HIE screening criteria increased from 13% to 16% ($p < 0.0001$), and the proportion of infants admitted to NICU for HIE evaluation increased from 1% to 1.4% ($p = 0.02$). There was no difference in the proportions of infants diagnosed with HIE (0.7% vs. 0.9%, $p = 0.3$) or treated with TH (0.2% vs. 0.3%, $p = 0.3$) between the two periods.

Statistical process control charts show a significant increase in the percentage of infants admitted to NICU for HIE evaluation in year 2021 (Figure 2) but no significant increase in the percentage of infants who received TH during pandemic years (Figure 3).

The maternal and infant demographics and clinical characteristics of the 131 cases that required NICU admission for HIE evaluation are shown in Table 2. During the COVID-19 period, there was an increase in maternal hypertension from 30% to 55% ($p = 0.006$). There were no differences in other pregnancy morbidities or delivery complications. Three mothers had asymptomatic or mild COVID-19 infection during pregnancy, and their newborns tested negative for SARS-Co-2 virus. During the COVID-19 period, there was a reduction in BW (−297 grams, $p = 0.005$) and a 7% increase in small for GA (SGA), although not statistically significant ($p = 0.09$). During the pre-COVID-19 period, six infants (11%) received chest compressions (CPR) compared to one infant (1%) in the COVID-19 period. Three of the six infants who received CPR had brief CPR for 30–60 s and were not intubated. One and five minute Apgar scores in the COVID-19 period were lower than the COVID-19 period. However, Apgar scores ≤5 were not different between the two periods. There was no difference in infants who had pH <7.0 in the CBG or first infant blood gas between the two periods, but there was an increase in infants with severe metabolic acidosis in the COVID-19 period (BD > 12 mEg/L: 22%–55%, $p < 0.0001$). There was no difference in abnormal neurological examination at one hour of life and multiorgan failure between the two periods. There were no

TABLE 1 Hypoxic ischemic encephalopathy screening and evaluation .

	Pre-COVID-19 (2018–2019)	COVID-19 (2020–2021)	*p*-value
Birth ≥35 weeks GA, *n*	N = 5,638	N = 5,318	
Cord blood gas obtained, *n* (%)	2,001 (35)	1,909 (36)	0.7
Cord/infant blood gas met screening criteria (pH ≥7.15 or BD ≥ 10), *n* (%)	733 (13)	851 (16)	**<0.0001**
Infants admitted to NICU for HIE evaluation, *n* (%)	54 (1)	77 (1.4)	**0.02**
Infants diagnosed with HIE, *n* (%)	38 (0.7)	45 (0.9)	0.3
Infants treated with therapeutic hypothermia, *n* (%)	12 (0.2)	18 (0.3)	0.3

GA, gestational age; HIE, hypoxic ischemic encephalopathy.
The bold values are statistically significant ($p < 0.05$).

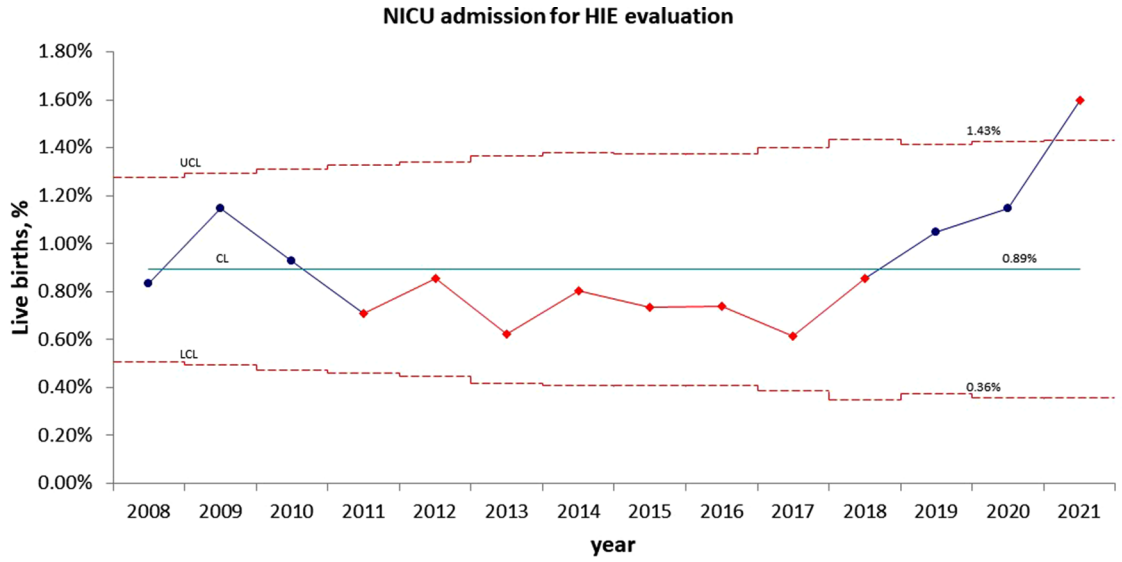

FIGURE 2
Statistical process control (p) chart shows the percent of infants admitted to NICU for evaluation of hypoxic ischemic encephalopathy (HIE) each year. The central line (solid) represents the mean and upper and lower control limit lines (dashed) represent 3 standard deviations from the mean.

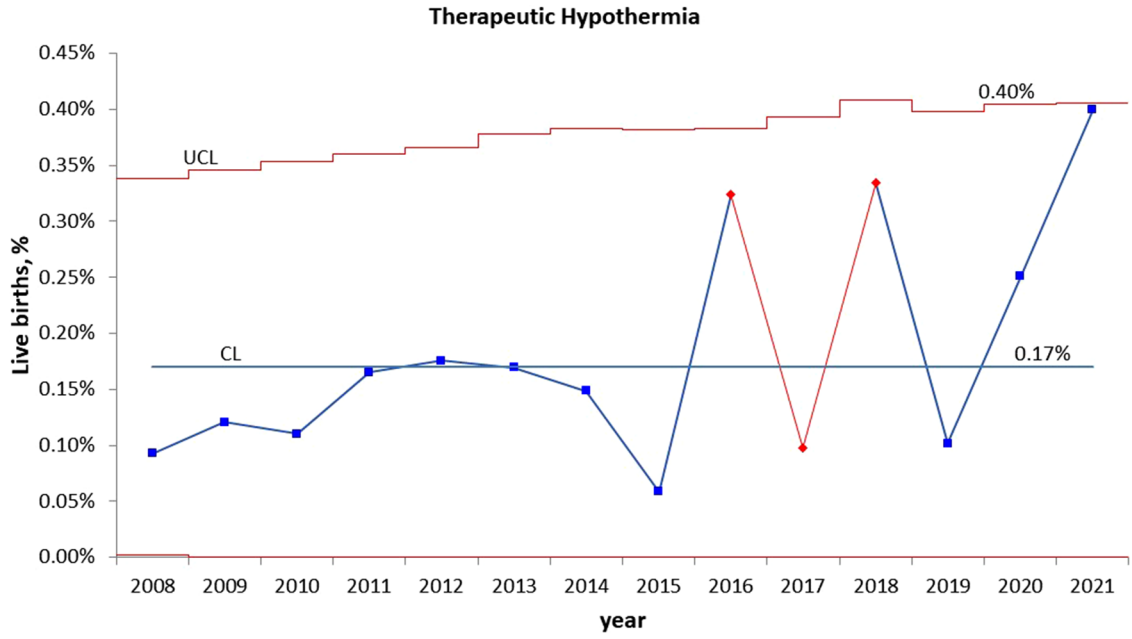

FIGURE 3
Statistical process control (p) chart shows the percent of infants treated with therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE) each year. The central line (solid) represents the mean and upper and lower control limit lines (dashed) represent 3 standard deviations from the mean.

differences in the HIE severity and short-term outcomes of the infants treated with TH between the two periods (Table 3).

Discussion

In this study, we examine the effect of COVID-19 on neonatal HIE and TH. During the COVID-19 pandemic, we observed a significant increase in maternal hypertension and infants with severe cord blood metabolic acidosis and abnormal neurological status at birth, resulting in a 40% increase in NICU admission for HIE evaluation. We did not find a significant difference in infants diagnosed with HIE or treated with TH between the two periods.

Universal screening of antenatal and perinatal risk factors for hypoxic-ischemic injury and recognition of the signs and symptoms of neonatal encephalopathy is essential for early identification and

TABLE 2 Infants admitted to NICU for hypoxic ischemic encephalopathy evaluation.

	Pre-COVID-19 (2018–2019) *N* = 54	COVID-19 (2020–2021) *N* = 77	*p*-value
Maternal Demographics			
Maternal age, Mean (SD)	31.1 (6.8)	31.4 (7.3)	0.8
Gravida, Median (IQR)	2 (1, 4)	3 (1.5, 4)	0.6
Para, IQR)	2 (1, 3)	2 (1, 3)	0.9
Multiples, *n* (%)	0	4 (5)	0.1
Hypertension, *n* (%)	16 (30)	42 (55)	**0.006**
Diatetes, *n* (%)	10 (19)	23 (30)	0.2
Thyroid disease, *n* (%)	2 (4)	3 (4)	0.7
COVID during pregnancy, *n* (%)		3 (4)	
Perinatal events			
Chorioamnionitis, *n* (%)	14 (26)	16 (21)	0.5
Abnormal Fetal Heart rate tracing, *n* (%)	18 (33)	27 (35)	0.8
Acute abruption, *n* (%)	3 (6)	2 (3)	0.3
Uterine Rupture, *n* (%)	1 (2)	0	0.4
Cord prolapse, *n* (%)	2 (4)	0	0.2
Shoulder dystocia, *n* (%)	3 (6)	2 (3)	0.3
Urgent/Emergency C/S, *n* (%)	26 (48)	30 (39)	0.3
Infant Demographics			
GA, week, Median (IQR)	39.1 (38, 40.4)	39.0 (37.7, 39.6)	0.08
Birth weight, gram, Mean (SD)	3,485 (631)	3,188 (548)	**0.005**
Male, *n* (%)	28 (52)	41 (53)	0.9
Small for gestational age <10% ile, *n* (%)	2 (4)	9 (12)	0.09
Large for gestational age >90% ile, *n* (%)	9 (17)	6 (8)	0.1
Delivery room outcomes			
DR Intubation, *n* (%)	4 (7)	3 (4)	0.3
DR Chest compressions, *n* (%)	6 (11)	1 (1)	**0.02**
1 min APGAR, Median (IQR)	3.5 (2, 6)	5 (2, 7)	**0.02**
5 min APGAR, Median (IQR)	6.5 (5, 8)	8 (6, 9)	**0.002**
5 min APGAR ≤5, *n* (%)	16 (30)	16 (21)	**0.2**
Critical cord or infant first hour blood gas			
pH <7, *n* (%)	20 (37)	36 (47)	0.3
BD ≥ 16 mmol/L, *n* (%)	14 (26)	41 (53)	**0.002**
BD ≥ 12 mmol/L, *n* (%)	22 (41)	55 (71)	**<0.0001**
Abnormal neurological examination >1 h of life, *n* (%)	70	58	0.9
Multiorgan injury, *n* (%)	13 (24)	15 (20)	0.5
Early onset of sepsis, *n* (%)	0	0	

GA, gestational age; DR, delivery room; BD, base deficit.
The bold values are statistically significant ($p < 0.05$).

TABLE 3 Characteristics and outcomes of infants treated with therapeutic hypothermia.

	Pre-COVID-19 (2018–2019) *N* = 12	COVID-19 (2020–2021) *N* = 18	*p*-value
HIE			
Mild, *n* (%)	4 (33)	4 (22)	0.7
Moderate and Severe, *n* (%)	8 (67)	14 (78)	
Seizures, *n* (%)	1 (8)	4 (22)	0.3
Brain MRI severity score, *n* (%)			
0	7 (58)	15 (83)	0.2
1	3 (25)	1 (6)	
2	1 (8)	0	
3	1 (8)	2 (11)	
Multiorgan injury, *n* (%)	8 (67)	10 (56)	0.5
Death (NICU), *n* (%)	1 (8)	0	0.4
LOS, day, Median (IQR)	9 (7.5, 19.5)	10.5 (7, 16)	0.8
At discharge, *n* (%)			
Abnormal Neuro exam	0	3 (17)	0.2
Anti-seizure medication	0	0	
G-tube	0	0	

HIE, hypoxic ischemic encephalopathy; LOS, length of stay.

initiation of TH for all eligible newborns (12, 37). Our institution developed and implemented a neonatal HIE screening protocol based on the published criteria for TH (6) in 2008. Between 2008 and 2020, our annual rates of infants admitted to NICU for evaluation of HIE were within the range of 0.6%–1.1%. The rates started to trend above the mean level in 2019. However, they did not become statistically significant until 2021, when the rate reached 1.6%. During 2019–2021, there were no practice changes in obstetric delivery management, pediatric DR resuscitation, or HIE screening. This change is likely related to the COVID-19 pandemic, which started in early 2020 in the US. The pandemic has had an unprecedented negative impact on public health and well-being. The adverse effect was more profound in racial and ethnic minority groups and people with lower socio-economic status. As a public safety-net hospital, over 70% of our pregnant mothers are Hispanic, and a majority of them with significant socio-economic disparities. The up trend in infants requiring HIE evaluation indicates a progressive increase in infants with severe metabolic acidosis and abnormal neurological status at birth. In 2021, the second year of the COVID-19 pandemic, the rate of HIE evaluation was significantly above the historical level, suggesting that women who experienced the negative impact of the pandemic during their entire pregnancy had worse birth outcomes.

Maternal hypertension may be a significant contributing factor to the increased rate of NICU admission for HIE evaluation during the pandemic. Maternal hypertension, if not well controlled, causes poor placental perfusion and fetal growth, which in turn increases the risk for fetal intolerance during labor, sentinel events, metabolic acidosis, birth asphyxia, hypoxic-ischemic injury and neonatal HIE (27–30, 38–40). According to the 2022 CDC report, the overall prevalence of maternal hypertension in the US was 14.6% during 2017–2019, and the prevalence in Hispanic women was 12.5% (41). Our institution's pre-COVID-19 (2018–2019) maternal hypertension rate was 22% and increased to 26% during the pandemic. Notably, the maternal hypertension rate for those requiring HIE evaluation increased from 30% in the pre-pandemic to 55% during the pandemic. The pandemic could have exacerbated maternal hypertension and negatively impacted newborns' metabolic and neurological status. There are multiple reasons for maternal hypertension increase during the pandemic. Our patient population experienced significant financial, physical, and mental stress. Their access to routine, in-person health services and prenatal care were interrupted. They had limited resources for adapting to changes in the health care system, including online health services. All these could have contributed to less monitoring and treatment of chronic diseases and

pregnancy-related complications. Similar to our study, Rao et al. (19) conducted a retrospective cohort study in a tertiary medical center in New York City, an epicenter of the pandemic. They found that women who delivered during the pandemic (27 March–31 May 2020) had a significantly higher rate of hypertensive disorders of pregnancy in maternal hypertension compared to women who delivered prior to the pandemic (27 March–31 May 2019) (OR = 1.05–1.85). Molina et al. (42) analyzed data from more than 1.6 million pregnant patients who gave birth in 463 US hospitals before and during the pandemic. They found a small but statistically significant increase in hypertensive disorders of pregnancy during the pandemic (OR, 1.04–1.08). A meta-analysis including 40 publications in 2020–2021 did not show a change in maternal hypertension during the pandemic (14). The discrepancy across the studies may reflect the difference in the timing and duration of studies, social environment due to infection control measures, and study populations.

Among the infants admitted to NICU for HIE evaluation, the average BW was significantly lower in the COVID-19 than in the pre-COVID-19 pandemic period (3,485 grams vs. 3,199 grams). The percentage of SGA infants increased from 2% in the pre-pandemic to 9% during the pandemic but was not statistically significant. BW is mainly determined by the duration of gestation and intrauterine growth. In this study, we included infants born at ≥35 weeks gestation, and the average GA of the infants admitted to NICU was not different between the two periods. Poor uteroplacental blood perfusion is the common pathophysiologic mechanism of intrauterine growth restriction (43–47). Furthermore, a fetus with placental insufficiency already suffers a baseline oxygen deficit at rest and has poor tolerance for labor. The superimposed hypoxic stress by uterine contractions during delivery can further worsen hypoxia and acidosis. In addition to maternal hypertension, other risk factors, such as, poor nutrition, prenatal maternal psychological distress (depression, anxiety, and stress) and substance use disorder, could have contributed to the low BW and SGA during the pandemic.

In our study, the pre-pandemic group had a higher rate of chest compressions. However, it only reflected six infants; three had brief chest compression and did not require intubation. The pre-pandemic group had less number of infants with severe metabolic acidosis but had overall low Apgar scores, even though the percentage of Apgar scores ≤5 was comparable to the pandemic period. Apgar scores and CBG are both commonly used in the newborn assessment (48, 49). CBG and acid-base balance, the most objective determinations of fetal hypoxia and metabolic condition at birth, are essential for diagnosing asphyxia and HIE (6, 48). The Apgar score provides an accepted and convenient method for reporting the status of the newborn infant immediately after birth and the response to resuscitation. While low Apgar scores may be one of the first indications of neonatal encephalopathy, its alone cannot be considered as the evidence or consequence of asphyxia. It does not predict individual neonatal mortality or neurologic outcome. In population-based studies, 5- and 10-minute Apgar scores ≥ five confer a clear increased risk of cerebral palsy (49). Several studies have shown a poor correlation between 1- and 5-minute Apgar scores and neonatal acid-base status (50–53). In addition to asphyxia, low Apagar scores can result from genetic diseases, congenital anomalies, maternal mediation during delivery, acute airway obstruction, as well as many other prenatal, perinatal, and postnatal factors that may not present with metabolic acidosis at birth. On the other hand, some neonates with reassuring Apgar scores still have a risk of CBG acidemia and poor birth outcomes (52, 54).

The global incidence of neonatal encephalopathy varies between 1 and 8 per 1,000 live births (1). Moderate/severe neonatal encephalopathy affects 0.5–3/1,000 live births in high-income countries, but higher in low- and middle-income countries (1, 55). In our patient population, the rate of HIE requiring TH has been relatively stable at 1–4/1,000 live births over the past 14 years. During the pandemic, the numbers of infants for HIE evaluation increased by 40% but the number of infants who met the diagnosed of HIE did not change significantly. This is because some infants who met the HIE screening criteria based on their cord blood acidosis had transient abnormal neurological examination, which was normalized within the first hour of life, hence were not diagnosed with HIE. While the severity and outcomes of the infants who were treated with TH were comparable between the two periods, the number of cases are very small. Few studies have assessed the impact of the COVID-19 pandemic on neonatal HIE. A single-center study found that more infants were diagnosed with HIE and treated with hypothermia during the first wave of the pandemic in Turkey (56). Similarly, a higher incidence of HIE was observed in a large NICU in the UK during the pandemic (57). Data from level-3 NICUs in the Canadian Neonatal Network (58). showed increased HIE and TH treatment during pandemic lockdown. However, the severity of HIE, associated morbidities, and mortality were not significantly different during the pandemic. Since this study used the hospital data from level-3 cooling centers, it is unclear whether the overall incidence of HIE, including mild HIE and their outcomes were affected by the pandemic.

TH is a standard of care therapy for infants with moderate and severe HIE. However, the risk-benefit balance of TH in mild HIE remains to be determined (37). In our study, mild HIE accounted for 33% and 22% of the TH cases in the pre-pandemic and pandemic periods, respectively. The decision to cool mild HIE cases was based on our evaluation protocol, which did not change during the study periods. In our practice, infants at risk for HIE but who do not meet the criteria for TH immediately after birth continue to be evaluated during the first five hours of life. TH treatment is used in infants with persistent mild abnormal or worsening neurological examinations, abnormal aEEG (with raw EEG tracing), or laboratory tests showing evidence of multiorgan injuries.

Our study has several limitations. It is a single-center retrospective study. While we observed a significant increase in NICU admission for HIE evaluation during the pandemic, other factors might have contributed to this change. It is important to continue monitoring the trend and identify other possible underlying causes for improving maternal and infant outcomes. Our sample sizes of HIE evaluation and TH are small. More studies with larger sample sizes are needed to confirm our findings.

Conclusion

During the COVID-19 pandemic, we observed a significant increase infants with severe metabolic acidosis and abnormal neurologic status at birth, resulting in an increased NICU admission for HIE evaluation. Increased maternal hypertension during the pandemic may be a significant contributing factor. The adverse effect of the COVID-19 pandemic on maternal morbidities may persist beyond the pandemic and should be closely monitored. While this single canter data did not show significant increases in neonatal HIE and the need for therapeutic hypothermia, larger studies and meta-analyses are needed for a comprehensive assessment of the impact of the COVID-19 pandemic on neonatal HIE.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Santa Clara Valley Medical Center Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DS: conceptualized and designed the study. SN, PJ and AH: facilitated data collection. PJ: performed data analysis, and PJ, DS, SN interpreted the results. DS: prepared the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Higher NICU admissions in infants born at ≥35 weeks gestational age during the COVID-19 pandemic

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Background: Increasing evidence has shown that the COVID-19 pandemic has had a profound negative impact on vulnerable populations and a significant effect on maternal and neonatal health. We observed an increase in the percentage of infants admitted to NICU from 8% to 10% in the first year of the pandemic. This study aimed to compare the delivery room outcomes, NICU admissions and interventions, and neonatal outcomes two years before and during the pandemic.

Methods: This was a retrospective study in a public hospital between pre-COVID-19 (April 2018–December 2019) and COVID-19 (April 2020–December 2021). Data were obtained from all live births at ≥35 weeks gestation (GA). Maternal and neonatal demographics, delivery room (DR), and NICU neonatal outcomes were compared between the study periods using simple bivariable generalized estimating equations (GEE) regression. Multivariable GEE logistic regression analysis was performed to adjust for the effects of baseline differences in demographics on the outcomes.

Results: A total of 9,632 infants were born ≥35 weeks gestation during the study period (pre-COVID-19 $n = 4{,}967$, COVID-19 $n = 4{,}665$). During the COVID-19 period, there was a small but significant decrease in birth weight (33 g); increases in maternal diabetes (3.3%), hypertension (4.1%), and Hispanic ethnicity (4.7%). There was a decrease in infants who received three minutes (78.1% vs. 70.3%, $p < 0.001$) of delayed cord clamping and increases in the exclusive breastfeeding rate (65.9% vs. 70.1%, $p < 0.001$), metabolic acidosis (0.7% vs. 1.2%, $p = 0.02$), NICU admission (5.1% vs. 6.4%, $p = 0.009$), antibiotic (0.7% vs. 1.7%, $p < 0.001$), and nasal CPAP (1.2% vs. 1.8%, $p = 0.02$) use. NICU admissions and nasal CPAP were not significantly increased after adjusting for GA, maternal diabetes, and hypertension; however, other differences remained significant. Maternal hypertension was an independent risk factor for all these outcomes.

Conclusion: During the COVID-19 pandemic period, we observed a significant increase in maternal morbidities, exclusive breastfeeding, and NICU admissions in infants born at ≥35 weeks gestation. The increase in NICU admission during the COVID-19 pandemic was explained by maternal hypertension, but other adverse neonatal outcomes were only partly explained by maternal hypertension. Socio-economic factors and other social determinants of health need to be further explored to understand the full impact on neonatal outcomes.

KEYWORDS

COVID-19 pandemic, neonatal intensive care unit (NICU) admission, maternal hypertension, metabolic acidosis, exclusive breastfeeding

Introduction

The COVID-19 pandemic due to SARS-CoV-2 infection has had profound negative impacts on vulnerable populations (1). The effect of the pandemic on population health has been more than the direct effect of the SARS-CoV-2 infection itself. The pandemic has indirectly impacted the socio-economic status of the population, limited access to healthcare systems, and worsened social determinants of health (2–4). There is a significant effect on the overall health of pregnant mothers and newborns (5).

Our institution has had one of the lowest NICU admission rates, at around 8%, in the state of California for the last decade. However, we observed an increase in the percentage of infants being admitted to the neonatal intensive care unit (NICU) in the first year of the pandemic to 10%. The increase in NICU admissions in 2020 led us to evaluate the impact of the COVID-19 pandemic on the outcomes of all the deliveries in our institution. Infants born at <35 weeks GA are admitted to NICU for prematurity according to our admission policy. We have previously shown that in our public safety net hospital, there was no change in our center's very preterm birth rate or very low birth weight in 2020, the first year of the pandemic (6). We focused on the delivery room (DR) and neonatal outcomes of infants born ≥35 weeks GA to understand the impact of the pandemic on term and late preterm infants.

The objective of this study was to compare the DR outcomes, NICU admissions and interventions, and neonatal outcomes in infants born two years before and during the COVID-19 pandemic and evaluate the effect of any changes in maternal morbidities on these outcomes.

Methods

This was a retrospective study comparing the DR and neonatal outcomes of all live births in a public hospital between the pre-COVID-19 period: 1 April, 2018–31 December 2019, and the COVID-19 pandemic period: 1 April 2020–31 December 2021. The rate of prematurity <37 weeks and <35 weeks gestational age (GA), and DR and NICU outcomes for infants born at ≥35 weeks GA were evaluated in detail to assess the impact of the COVID-19 pandemic on these infants. The study was approved by the Institutional Review Board.

Newborn care practices

Infants born at <35 weeks GA or with birth weight <1,800 grams were routinely admitted to NICU for neonatal care. In the DR, the goal was to clamp the umbilical cord after three minutes to optimize neonatal transition and placental transfusion. The Umbilical cord was clamped earlier than three minutes if the infant was not breathing by one minute despite the initial steps of newborn care or if there was maternal hemorrhage. All stable infants ≥35 weeks GA were placed on mothers' chest for skin-to-skin in the DR. Skin-to-skin care was uninterrupted for the first hour to promote bonding and breastfeeding. Newborns roomed-in with the mothers in the postpartum unit at all times. Infants who required respiratory support, intravenous fluids, antibiotics, or those who had severe metabolic acidosis, abnormal neurological examination, or major anomalies were admitted to NICU for further evaluation and treatment.

COVID-19 pandemic changes

Our institution implemented universal SARS-CoV-2 screening of all pregnant women who were admitted for delivery in April 2020 (7). From October 2020, women who tested positive within 90 days prior to admission for delivery and did not have new symptoms of COVID were not retested at the time of delivery. If the mother's infection was within 10–14 days of delivery, the mother and infant roomed in together with airborne isolation precautions, with the mother wearing a surgical mask when holding and breastfeeding the baby during the isolation period. Skin-to-skin and breastfeeding were encouraged. The infants born to mothers who were in the intensive care unit or too sick to care for their infant were separated from the mother and cared for by another healthy family member. There was no change in the NICU admission criteria or other NICU care practices during the pandemic.

The hospital visitation policy was restricted to one support person for the mother during the delivery process and in the postpartum unit. The NICU visitation policy was also restricted to only one designated parent at the beginning of the pandemic and six months later expanded to include both parents but only one parent at the bedside at a time. Parents were not allowed to visit NICU during the SARS-CoV-2 isolation period if they were positive or during the quarantine period if they were exposed. The lactation consultant coordinated the delivery of the mother's own milk when the parents were in isolation or quarantine. The parents were able to see their infant via web camera and communicate with the NICU staff via phone.

Data collection

Data were obtained from automated reports and chart reviews for all births from hospital electronic health records. Data for all NICU admissions were obtained from the NICU database that is maintained for mandated NICU data submissions and quality improvement projects. The maternal demographics included age, gravida, para, maternal diabetes, hypertension, pre-pregnancy BMI, race and ethnicity, SARS-CoV-2 infection, chorioamnionitis; DR outcomes included delivery type, cord blood gas values, duration of delayed cord clamping (DCC), APGAR scores, DR intubation, and chest compressions; neonatal demographics included GA, birth weight, and sex; and neonatal outcomes included any breastfeeding, exclusive breastfeeding, NICU admissions, reasons for NICU admission, and NICU

interventions including antibiotics use, respiratory support including mechanical ventilation, continuous positive airway pressure (CPAP), non-invasive mechanical ventilation (NIMV), inhaled nitric oxide (iNO), and blood transfusions.

Analysis

Maternal and neonatal demographics, DR, and NICU neonatal outcomes were compared between the study periods using simple bivariable generalized estimating equations (GEE) regression models clustered around unique pregnancies to account for multiples (i.e., twins, triplets, etc.). Gaussian, Poisson, and logistic GEE models were used for continuous, count, and binary outcomes, respectively. Multivariable GEE logistic regression analysis was performed to adjust for the effects of baseline differences in demographics on the outcomes. All GEE models utilized independent within-group correlation structures and robust variance estimates. Data analysis was performed using Stata 17.0 (Stata Corp, College Station, TX) and p-value <0.05 was considered significant.

Results

A total of 9,632 were born at ≥35 weeks GA (pre-COVID-19 $n = 4{,}967$, COVID-19 $n = 4{,}665$) and included in the study. There was no difference in the rate of prematurity <35 weeks GA (3.5% vs. 4.0%, $p = 0.2$) between the two study periods. The demographics and DR outcomes data are shown in Table 1. During the COVID-19 period, there was a small but statistically significant decrease in birth weight (33 g) of infants born at ≥35 weeks gestation. There was no difference in maternal age, gravida, or parity between the study periods, but there were significant increases in maternal diabetes (21.2% vs. 24.5%), maternal hypertension (21.9% vs. 25.9%), and Hispanic ethnicity (68.4% vs. 73.1%) during the pandemic. During the pandemic, 4% of the mothers in this study were SARS-CoV-2 positive during pregnancy.

TABLE 1 Demographics.

	2018–2019 (Pre-COVID-19)	2020–2021 (COVID-19)	Difference (95% CI)	p-value
Liveborn infants ≥35 weeks GA, *n*	4,967	4,665		
Infant demographics				
Gestational age, weeks, mean (SD)	39.2 (1.3)	39.0 (1.2)	-0.2 (−0.3, −0.2)	<0.001
Birth weight, grams, mean (SD)	3,355 (489)	3,322 (482)	−33 (−53, −13)	0.001
Male sex, *n* (%)	2,524 (50.8)	2,382 (51.1)	0.2 (−1.8, 2.3)	0.8
Maternal demographics				
Age, mean (SD)	29.6 (6.2)	29.4 (6.3)	−0.1 (−0.4, 0.1)	0.3
Gravida, median (IQR)	2 (1, 4)	2 (1, 4)	0.0 (−0.1, 0.1)	0.9
Parity, median (IQR)	2 (1, 3)	2 (1, 3)	0.0 (0.0, 0.1)	0.2
Multifetal pregnancies, *n* (%)	106 (2.1)	104 (2.2)	0.1 (−0.7, 0.9)	0.8
Twins, *n* (%)	100 (2.0)	104 (2.2)		
Triplets, *n* (%)	6 (0.1)	0 (0)		
Diabetes, *n* (%)[a]	1,049 (21.2)	1,137 (24.5)	3.3 (1.6, 5.0)	<0.001
Gestational, *n* (%)	935 (18.9)	1,066 (23)		
Pre-gestational, *n* (%)	114 (2.3)	71 (1.5)		
Hypertension, *n* (%)[a]	1,089 (22.0)	1,210 (26.1)	4.1 (2.4, 5.9)	<0.001
Gestational, *n* (%)	413 (8.3)	517 (11.1)		
Chronic, *n* (%)	112 (2.3)	147 (3.2)		
Pre-eclampsia/Eclampsia, *n* (%)	564 (11.4)	546 (11.8)		
Body mass index, mean (SD)[b]	27.9 (6.7)	28.2 (6.6)	0.2 (0.0, 0.5)	0.09
Race and ethnicity				<0.001
Hispanic, *n* (%)	3,399 (68.4)	3,412 (73.1)		
Asian, *n* (%)	736 (14.8)	546 (11.7)		
White, *n* (%)	418 (8.4)	328 (6.9)		
Black, *n* (%)	248 (5.0)	199 (4.3)		
Multiracial, *n* (%)	92 (1.9)	91 (2.0)		
Pacific Islander, *n* (%)	37 (0.7)	31 (0.7)		
Unknown, *n* (%)	27 (0.5)	56 (1.2)		
Native American, *n* (%)	8 (0.2)	9 (0.2)		
Other, *n* (%)	2 (0.0)	1 (0.0)		
Chorioamnionitis, *n* (%)	405 (8.2)	392 (8.5)	0.3 (−0.8, 1.4)	0.6
Cesarean section, *n* (%)	1,332 (26.8)	1,249 (26.8)	0.0 (−1.9, 1.8)	1.0
SARS-CoV-2 infection, *n* (%)	0 (0)	186 (4)	n/a	n/a

[a]A total of 10 patients from Pre-COVID-19 and 26 patients from COVID-19 period were excluded from difference analysis due to missing data.
[b]A total of 187 patients from Pre-COVID-19 and 272 patients from COVID-19 period were excluded from difference analysis due to missing data.

Delivery room outcomes

There was a decrease in infants who received at least one minute DCC (96.3% vs. 95.1%), and completed three minutes DCC (78.1% vs. 70.3%), but an increase in the severe metabolic acidosis (base deficit ≥16) (0.7% vs. 1.2%) in umbilical cord gas during the pandemic as shown in Table 2. The increase in severe metabolic acidosis remained significant even after adjusting for baseline differences in GA, maternal diabetes, and hypertension. There was no change in the APGAR scores, DR intubation, or cardiac medications between the study periods.

Neonatal outcomes

There was a significant increase in the exclusive breastfeeding rate (65.9% vs. 70.1%) and NICU admissions (5.1% vs. 6.4%) during the COVID-19 pandemic period. The frequency of NICU admissions, admission diagnosis, and NICU interventions are shown in Table 2. There was a significant increase in infants admitted to NICU for evaluation of hypoxic ischemic encephalopathy (HIE) (1% vs. 1.5%) and evaluation for sepsis (0.4% vs.0.9%) during the pandemic. There was an increase in the use of antibiotics (0.7% vs. 1.7%) and nasal CPAP (1.2% vs. 1.8%) during the COVID-19 pandemic period. The increases in overall NICU admissions and nasal CPAP were not significant after adjusting for baseline differences in GA, maternal diabetes, and maternal hypertension, however NICU admission for evaluation of HIE, evaluate for sepsis, and antibiotic use remained significant even after adjusting for the baseline differences (Table 3). Maternal hypertension was independently associated with an increase in the risk of NICU admission, NICU antibiotic, CPAP, and a decrease in the exclusive breastfeeding rate.

Discussion

In this single-center study, during the COVID-19 pandemic period, we observed an increase in maternal morbidities like hypertension and diabetes, severe metabolic acidosis in cord blood, exclusive breastfeeding, NICU admissions, and use of

TABLE 2 Delivery room and neonatal outcomes.

	2018–2019 (Pre-COVID-19)	2020–2021 (COVID-19)	Difference (95% CI)	*p*-value
Livebirths ≥ 35 weeks GA, *n*	4,967	4,665		
Delivery room outcomes				
DCC duration seconds, median (IQR)	180 (180, 180)	180 (150, 180)	−8.0 (−9.8, −6.1)	<0.001
DCC ≥60 s, *n* (%)[a]	4,619 (96.3)	4,333 (95.1)	−1.2 (−2.1, −0.4)	0.003
DCC ≥180 s, *n* (%)[a]	3,746 (78.1)	3,204 (70.3)	−7.8 (−9.6, −6.0)	<0.001
Apgar @ 1 min <4, *n* (%)	72 (1.5)	90 (1.9)	0.5 (0.0, 1.0)	0.07
Apgar @ 5 min <8, *n* (%)	119 (2.4)	125 (2.7)	0.3 (−0.3, 0.9)	0.4
DR intubation, *n* (%)	4 (0.1)	4 (0.1)	0.0 (−0.1, 0.1)	0.9
Chest compression, *n* (%)	7 (0.1)	0 (0.0)	n/a	n/a
Delivery room epinephrine, *n* (%)	1 (0.0)	0 (0.0)	n/a	n/a
Cord gas pH < 7, *n* (%)	38 (0.8)	51 (1.0)	0.3 (−0.1, 0.7)	0.1
Cord gas base deficit ≥16, *n* (%)	36 (0.7)	56 (1.2)	0.5 (0.1, 0.9)	0.02
Neonatal outcomes				
Any breastfeeding, *n* (%)	4,844 (97.5)	4,543 (97.4)	−0.1 (−0.8, 0.5)	0.7
Exclusive breastfeeding, *n* (%)	3,271 (65.9)	3,271 (70.1)	4.3 (2.4, 6.2)	<0.001
NICU admissions, *n* (%)	255 (5.1)	299 (6.4)	1.3 (0.3, 2.2)	0.009
NICU admission diagnosis				
Evaluation for HIE, *n* (%)	48 (1.0)	71 (1.5)	0.6 (0.1, 1.0)	0.02
Therapeutic hypothermia, *n* (%)	9 (0.2)	18 (0.4)	0.2 (0.0, 0.4)	0.06
Hypoglycemia, *n* (%)	16 (0.3)	18 (0.4)	0.1 (−0.2, 0.3)	0.6
Respiratory distress, *n* (%)	118 (2.4)	127 (2.7)	0.3 (−0.3, 1.0)	0.3
Evaluation for sepsis, *n* (%)	21 (0.4)	41 (0.9)	0.5 (0.1, 0.8)	0.006
Early onset sepsis, *n* (%)	0 (0.0)	1 (0.0)	n/a	n/a
NICU interventions				
Antibiotics, *n* (%)	36 (0.7)	80 (1.7)	1.0 (0.5, 1.4)	<0.001
Respiratory support, *n* (%)	107 (2.1)	121 (2.6)	0.4 (−0.2, 1.1)	0.2
Nasal CPAP, *n* (%)	59 (1.2)	82 (1.8)	0.6 (0.1, 1.1)	0.02
Nasal IMV, *n* (%)	6 (0.1)	8 (0.2)	0.1 (−0.1, 0.2)	0.5
Intubation, *n* (%)	13 (0.3)	15 (0.3)	0.1 (−0.2, 0.3)	0.6
Inhaled nitric oxide, *n* (%)	3 (0.1)	9 (0.2)	0.1 (0.0, 0.3)	0.07
Transfusion, *n* (%)	10 (0.2)	14 (0.3)	0.1 (−0.1, 0.3)	0.3

[a]A total of 171 patients from Pre-COVID-19 and 107 patients from COVID-19 period were excluded from difference analysis due to missing data.

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TABLE 3 Multivariate regressions analysis.

Outcome	Predictors	Odds ratio	95% CI	*p*-value
Exclusive breastfeeding				
	Study period	1.33	1.22–1.46	<0.001
	Gestational age, days	1.28	1.24–1.33	<0.001
	Maternal diabetes	0.75	0.68–0.83	<0.001
	Maternal hypertension	0.62	0.56–0.69	<0.001
NICU admission				
	Study period	1.16	0.97–1.39	0.09
	Gestational age, days	0.68	0.63–0.73	<0.001
	Maternal diabetes	1.10	0.90–1.34	0.4
	Maternal hypertension	1.80	1.49–2.18	<0.001
Evaluation for HIE				
	Study period	1.51	1.05–2.17	0.03
	Gestational age, days	0.95	0.82–1.10	0.5
	Maternal diabetes	1.13	0.75–1.68	0.6
	Maternal hypertension	2.28	1.57–3.32	<0.001
Cord gas base deficit ≥16				
	Study period	1.58	1.04–2.40	0.03
	Gestational age, days	1.00	0.84–1.19	1.0
	Maternal diabetes	1.02	0.62–1.66	0.9
	Maternal hypertension	3.14	2.04–4.83	<0.001
Evaluation for sepsis				
	Study period	2.07	1.21–3.52	0.008
	Gestational age, days	1.05	0.80–1.38	0.7
	Maternal diabetes	0.77	0.41–1.43	0.4
	Maternal hypertension	2.01	1.17–3.47	0.01
NICU antibiotic use				
	Study period	2.25	1.52–3.35	<0.001
	Gestational age, days	0.72	0.61–0.85	<0.001
	Maternal diabetes	0.74	0.47–1.16	0.2
	Maternal hypertension	1.73	1.16–2.57	0.007
NICU CPAP				
	Study period	1.36	0.96–1.91	0.08
	Gestational age, days	0.62	0.53–0.72	<0.001
	Maternal diabetes	1.15	0.79–1.67	0.5
	Maternal hypertension	1.59	1.09–2.33	0.02

antibiotics, and respiratory support in infants born at ≥35 weeks GA and a decrease in three minutes DCC.

Maternal morbidities

In our study, we observed a significant increase in maternal hypertension and diabetes during the pandemic. The baseline rate of maternal hypertension in the United States in 2019 was 16%, up from 13% in 2017 (8). In our study, the baseline maternal hypertension was already at 22%, much higher than that reported nationally. Many systematic reviews and meta-analyses have shown an increased risk of pre-eclampsia in pregnant mothers who had SARS-CoV-2 infection (9–11), with the risk being higher in those with symptomatic infection compared to asymptomatic and with severe infections (12, 13). The rate of SARS-CoV-2 infection in our study was relatively low, and a majority of those were identified due to asymptomatic screening. Despite the low SARS-CoV-2 infection rate, we had a significant increase in the rate of hypertension and diabetes in our study population.

The increase in maternal hypertension and diabetes in our study may be attributable to multiple factors such as decreased physical activity due to the shelter in place and remote work, significant impact on the socio-economic factors leading to stress, and increasing disparities for the marginalized population, including minorities. There was a significant decrease in access to care for all patients, including prenatal care worldwide. Even though telehealth was widely implemented, reports have shown decreases in overall care. The increase in maternal morbidities has been reported both nationally and internationally. There has been an increase in maternal hypertension and diabetes reported in North American epicenters of the pandemic (14–16). A Chinese study showed that pregnant women who experienced lockdown had an increase in HbA1C in those with gestational diabetes and an increase in pregnancy-induced hypertension in normoglycemic women (17). Italian studies also have shown an increase in gestational diabetes during the pandemic (18, 19). An Israeli study showed an increase in both hypertension and gestational diabetes during the pandemic (20). Another study from France showed that the glycemic control in GDM was poor during the pandemic (21). Other studies and a meta-analysis have shown a similar increase in gestational diabetes during the pandemic (22), especially in the Hispanic population (23). However, studies from France and Australia have not shown an increase in maternal diabetes or hypertension during or after the pandemic lockdown (24, 25).

Delivery room outcomes

The increase in maternal morbidities has a negative effect on newborns. Maternal hypertension and diabetes both affect fetal well-being during labor. In our study, there was an increase in metabolic acidosis in the cord blood during the pandemic, and maternal hypertension was associated with three times the odds of severe metabolic acidosis. Other studies that have reported on cord gas values during the pandemic have not shown any difference (24, 26). One major difference between our study and the multicenter study from France (24) is the prevalence of maternal hypertension: their baseline hypertension was 5.4% compared to 22% in our study. Moreover, in contrast to a 4% increase in maternal hypertension in our study, there was no increase in their study.

In our center, the goal is to wait three minutes before clamping the cord if the infant is breathing by one minute of life and there is no concern for maternal bleeding. The decrease in the proportion of infants receiving three minutes of DCC is indirect evidence of suboptimal fetal/neonatal transition or a decrease in the well-being of the mother at the time of birth.

NICU admissions

NICU admissions increased in the ≥35weeks GA population in our study during the pandemic. A systematic review of 38 studies

evaluating the impact of the mitigation efforts against COVID-19 showed that there was a decrease in NICU admissions (27). Other studies have shown no change in NICU admissions (24, 28) and specifically a decrease in NICU admissions (29–31) for term infants during the COVID-19 pandemic. Differences in patient demographics may explain the differences between our study and others: we have a higher maternal hypertension rate (22%–26%), number of Hispanics (68%–73%), and majority of our patients are on public insurance. The negative effects of the pandemic were higher in the disadvantaged population, which adds to the worsening of the maternal and neonatal health outcomes in this population. An observational cohort study from UK neonatal research network showed a decrease in overall NICU admissions during the pandemic compared to the same time during the previous seven years. However, they did show an increase in transfer to higher level NICU in term infants during the pandemic (30).

Exclusive breastfeeding

Encouragingly, we observed an increase in the exclusive breastfeeding rate during the study period. Similarly, observational studies from the UK research network and Spain showed an increase in the breastfeeding rate at discharge in term infants during the pandemic (30, 32). Many other studies have shown a decrease or plateauing in breastfeeding rate during the pandemic (28, 33–38). One study showed that there was no difference in breast milk feeding in those on public insurance compared to an increase in breastfeeding rates in those with private insurance (39). Despite the majority of our patient population being on public insurance, we showed an increase in the breastfeeding rate. The pandemic has had direct and indirect consequences on breastfeeding. During the lockdown, many face-to-face professional and peer supports were reduced. A survey from 2021 showed 42% of mothers felt breastfeeding was protected due to the lockdown, however, 27% of mothers struggled to get support and numerous barriers stemming from the lockdown, resulting in earlier cessation of breastfeeding (40). A published narrative review in 2021 included 12 studies looking at breastfeeding plans in women during the pandemic (41). Mothers reported positive breastfeeding experiences when they perceived more time for motherhood and negative breastfeeding experiences when mothers were separated from their newborns and had decreased family and professional support. In a recent study, Gribble et al. evaluated the guidelines around breastfeeding in mothers with SARS-CoV-2 infection from 101 countries (42). Despite WHO's strong recommendation early in the pandemic supporting skin-to-skin, breastfeeding, and rooming in with mothers with COVID-19, less than a quarter of the guidelines recommended them. In our institution, mothers who were positive for SARS-CoV-2 were counseled extensively on the benefits of breastfeeding and proper respiratory hygiene while breastfeeding and were given the option of having their infant room-in with them. Every one of them chose to room-in with their infant. The continued hands-on lactation support for all mothers during their hospital stay allowed for successful breastfeeding in all newborns, including those who were born to mothers positive for SARS-CoV-2 infection at the time of birth. Some of the visitation restrictions in the post-partum unit may have allowed the staff to spend more time with mothers supporting breastfeeding and uninterrupted time for the mother to breastfeed the newborn.

One limitation of our study is that it is from a single center. However, our findings should be generalizable to other public safety net hospitals that serve similar patient populations.

Conclusion

During the COVID-19 pandemic period, we observed a significant increase in maternal morbidities and NICU admissions in infants born at ≥35 weeks gestation. The increase in NICU admissions during the COVID-19 pandemic was explained by maternal hypertension, but other adverse neonatal outcomes were only partly explained by an increase in maternal hypertension. Other socio-economic factors and social determinants of health need to be further explored to understand the full impact of the COVID-19 pandemic on neonatal outcomes. We also observed an increase in the exclusive breastfeeding rate during the pandemic, which is encouraging and likely attributable to uninterrupted lactation services in the postpartum unit to support breastfeeding.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional review board of Santa Clara Valley Medical Center. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

PJ and DS: conceptualized and designed the study. SN and AH: facilitated data collection. PJ and MN: performed data analysis. PJ, DS, and SN interpreted the results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A multicentre study on the clinical characteristics of newborns infected with coronavirus disease 2019 during the omicron wave

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Objective: To investigate the clinical characteristics and outcomes of newborns infected with coronavirus disease 2019 (COVID-19) during the Omicron wave.
Methods: From December 1, 2022, to January 4, 2023, clinical data were collected from neonates with COVID-19 who were admitted to 10 hospitals in Foshan City, China. Their epidemiological histories, clinical manifestations and outcomes were analysed. The neonates were divided into symptomatic and asymptomatic groups. The *t* test or χ^2 test was used for comparisons between groups.
Results: A total of 286 children were diagnosed, including 166 males, 120 females, 273 full-term infants and 13 premature infants. They were 5.5 (0–30) days old on average when they were admitted to the hospital. These children had contact with patients who tested positive for COVID-19 and were infected through horizontal transmission. This study included 33 asymptomatic and 253 symptomatic patients, among whom 143 were diagnosed with upper respiratory tract infections and 110 were diagnosed with pneumonia. There were no severe or critical patients. Fever (220 patients) was the most common clinical manifestation, with a duration of 1.1 (1–6) days. The next most common clinical manifestations were cough with nasal congestion or runny nose (4 patients), cough (34 patients), poor appetite (7 patients), shortness of breath (15 patients), and poor general status (1 patient). There were no significant abnormalities in routine blood tests among the neonates infected with COVID-19 except for mononucleosis. However, compared with the asymptomatic group, in the symptomatic group, the leukocyte and neutrophil granulocyte counts were significantly decreased, and the monocyte count was significantly increased. C-reactive protein (CRP) levels were significantly increased (≥10 mg/L) in 9 patients. Myocardial enzyme, liver function, kidney function and other tests showed no obvious abnormalities.
Conclusions: In this study, neonates infected with the Omicron variant were asymptomatic or had mild disease. Symptomatic patients had lower leucocyte and neutrophil levels than asymptomatic patients.

KEYWORDS

neonates, coronavirus disease 2019, omicron wave, clinical features, routine blood tests

Introduction

The coronavirus disease 2019 (COVID-19) pandemic that started in 2019 spread worldwide, and the COVID-19 epidemic in China is still ongoing. In particular, at the end of 2022, the Omicron variant spread to mainland China. The rapid spread of COVID-10 posed a great threat to a vast number of adults, children and newborns (1, 2). Some studies have shown that infection with COVID-19 is not commonly observed in hospitalized newborns (3). The majority of newborns have mild clinical manifestations and only require short-term hospitalization for treatment and most newborns present with symptoms of fever, upper respiratory tract infections, and lower respiratory tract infections (4). Multiple studies from different countries and regions and a meta-analysis have shown that the typical clinical manifestations of children with COVID-19 infection are fever, cough, and shortness of breath (1, 2, 5). Some studies have shown that common symptoms in newborns after contracting COVID-19 include shortness of breath and fever, and most newborns who are infected with the virus are asymptomatic or have mild symptoms and do not require respiratory support (6, 7). Another study showed that the most common symptoms observed in newborns infected with COVID-19 were fever, feeding intolerance, and cough, with myocarditis being the most common complication in those with severe-critical illness (8).

Previous studies showed that after COVID-19 infection, newborns generally had only mild clinical manifestations and did not need special treatment (9, 10). Nevertheless, certain studies have revealed severe scenarios. For instance, a study conducted in Brazil revealed that neonates who contracted COVID-19 during the initial phase of the pandemic experienced more severe clinical manifestations, which led to higher mortality rates. Such newborns displayed accelerated disease progression, longer hospital stays, and more pronounced respiratory distress, laryngospasm, and cough (11). Laboratory tests indicated a normal range of white blood cells and reduced lymphocyte levels (1, 2, 5, 6). However, newborns often have abnormal test results and imaging findings, including positive results for neutropenia and/or mononucleosis but not lymphocytopenia (12). There are also studies reporting that after infection with COVID-19, a reduction in platelet, lymphocyte, haemoglobin, eosinophil, and basophil counts and an increase in the neutrophil count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio were commonly observed, and these indicators were associated with clinical prognosis (13, 14).

The clinical presentation and severity of COVID-19 have changed with the emergence of the Alpha, Beta, Delta and Omicron SARS-CoV-2 variants in different infection waves. Most published studies of neonatal COVID-19 infection were conducted before the Omicron wave. There is limited information on the clinical characteristics of neonatal COVID-19 infection caused by the Omicron variant. In this study, the data of neonates with COVID-19 who were admitted to 10 hospitals in Foshan from December 1, 2022, to January 4, 2023, were collected and analysed to investigate clinical characteristics and outcomes to provide some reference for the prevention and management of Omicron among newborns during the epidemic.

Methods

Study design and population

During the Omicron variant wave, it is recommended that all hospitalized newborns undergo routine COVID-19 testing. Furthermore, if a mother exhibits any symptoms of a respiratory tract infection, such as fever or cough, her newborn must be closely monitored in the maternal-child ward and undergo COVID-19 testing. Between December 1, 2022, and January 4, 2023, 286 neonates infected with COVID-19 were admitted to 10 hospitals. These newborns infected with COVID-19 were in the same room as their mothers after birth. If these newborns develop respiratory symptoms such as cough and fever, they should be admitted to the neonatology department for further observation. If a mother has symptoms of respiratory tract infection or has a history of contact with COVID-19-positive patients, the mother needs to take protective measures such as wearing a mask and washing hands before contact with children.

The inclusion criteria were as follows: (1) full-term infant age <28 days, preterm infant corrected gestational age <40 weeks; (2) pharyngeal swab results of COVID-19 nucleic acid test were positive or antigen-positive. Ethics approval was obtained from Foshan Maternity and Child Healthcare Hospital (approval number: FSFY-MEC-2023-022) in accordance with the Declaration of Helsinki.

There were a total of 13 premature infants included in this study. Any infant whose corrected gestational age exceeded 40 weeks did not meet our admission criteria for the neonatology department.

Pharyngeal swab test for COVID-19

Pharyngeal swab samples were analysed at COVID-19 laboratories in several participating hospitals. The main kit used was the novel coronavirus pneumonia Nucleic Acid Detection Kit of Wuhan Mingde Biotechnology Co., Ltd. (National Instrument Note 20203400212), which uses PCR-fluorescence probe technology for detection. The procedures were performed according to the technical specifications and quality control specifications of the China National Clinical Laboratory Center.

Antigens in throat swab samples were detected by the Novel Coronavirus (2019-nCoV) Antigen Detection Kit (colloidal gold method) of Xiamen Aode Biotechnology Co., Ltd. The results are analysed as follows: if two dark or light red or purple bands appear, one in the testing area (T) and the other in the quality control area (C), this indicates a positive result. If only one red or purple band appears in the quality control area (C) and no band appears in the detection area (T), this indicates a negative result. If there is no red or purple band in the quality control area (C), regardless of whether there is a band in the detection area (T), the result is invalid, and retesting is necessary.

Clinical data collection

The hospitalized neonates were registered, and information such as sex, age, gestational age, birth weight, epidemiological history,

clinical symptoms, laboratory results, imaging results, treatment and length of stay were collected, and a clinical database was established.

Clinical diagnosis and classification

The COVID-19 Pneumonia (Trial Version 9) criteria issued by the National Health Commission are used for the diagnosis and classification of cases (15). Asymptomatic infection was defined as those whose nucleic acid test met the diagnostic criteria but without any symptoms or signs; mild infection was defined as only mild clinical manifestations without imaging manifestations of pneumonia. Clinical and imaging manifestations of pneumonia were considered signs of general infection. Severe infection was defined as persistent high fever for more than 3 days, shortness of breath, hypoxemia, dyspnoea, lethargy, convulsion, food resistance or feeding difficulty with significant imaging findings of pulmonary inflammation. A critical infection was defined as secondary respiratory failure requiring respiratory support, shock, or a combination of other organ failures. The date when symptoms of COVID-19 infection appeared and the nucleic acid or COVID-19 antigen result was positive was considered the onset date.

Discharge criteria

According to the discharge conditions stated in the Perinatal and Neonatal COVID-19 Infection Prevention and Control Plan (third edition), patients could be discharged once the patient's condition was stable, vital signs such as respiration and body temperature were normal, feeding tolerance was achieved, the family could provide reasonable care, and the discharge criteria were met (16, 17).

Statistical analysis

We used SPSS 20.0 for statistical analysis, and measurement data are expressed as $\bar{x} \pm S$, minimum values and maximum value if necessary. Comparisons between groups were performed by t test or t'. The chi-square test or Fisher's exact probability method was used to compare the groups based on the statistical data. A bilateral value of $P < 0.05$ was considered statistically significant.

Results

Most of the 286 patients had a contact history with family members who were positive for COVID-19. There were 166 male and 120 female patients, including 13 premature infants. Of the 286 newborns infected with COVID-19, 39 patients lacked data on amniotic fluid status. These infants had an average gestational age of 38.7 (29–41) weeks and an average birth weight of 2,949.4 ± 971.9 g. In total, 97 of the newborns were delivered by caesarean section, and 189 patients were delivered naturally. At admission, the average age of the patients was 5.5 (0–30) days. Among them, 134 newborns were exclusively breastfed, 14 newborns were fed formula, and 138 newborns received mixed feeding, as shown in Table 1.

Chest x-ray was performed for 227 patients; 64 patients showed no abnormality or thickened texture, 6 patients showed bronchitis-like changes, 157 (110 patients diagnosed with pneumonia and 47 who did not meet the diagnostic criteria for pneumonia) patients showed pneumonia-like changes, and 2 were diagnosed with pneumonia by chest CT examination. All children were given routine symptomatic treatment after admission and were discharged after their condition improved. The median length of stay was 5.6 (2–13) days.

Clinical manifestations

Patients with fever, cough, nasal congestion or gastrointestinal symptoms were all regarded as symptomatic infected persons. There were 253 (88.5%) newborns with symptoms (Table 2). Among the children with symptomatic infection, 143 patients had mild infection, and 110 patients had common infections, such as fever (220 cases), cough with nasal congestion or runny nose (4 cases), cough (34 cases), poor appetite (7 cases), shortness of breath (15 cases), and poor general status (1 case). Fever was the most common clinical manifestation of COVID-19 infection, with fever occurring in 220 patients (76.9%), while 66 patients (23.1%) did not have a fever. Of those with fever, 181 had symptoms of fever alone. Some newborns exhibited

TABLE 1 Baseline characteristics of neonates infected with COVID-19.

Variables	Asymptomatic group ($n = 33$)	Symptomatic group ($n = 253$)	t or χ^2	P
Gender				
Male	22 (66.7)	144 (56.9)	1.14	0.286
Female	11 (33.3)	109 (43.1)		
Gestational age	38.1 ± 2.0	38.6 ± 1.3	−1.48	0.160
Birth weight	3,005.0 ± 864.5	3,143.0 ± 637.1	−1.06	0.289
Mode of delivery				
Spontaneous delivery	23 (69.7)	166 (65.6)	0.22	0.641
Caesarean section	10 (30.3)	87 (34.4)		
Amniotic fluid				
Clear	22 (71)	186 (86.1)	12.62	0.013
Maternal risk factors	22 (66.7)	156 (60.9)	3.22	0.2
Yes	10 (30.3)	100 (39.1)		
Feeding pattern				
Breast-feeding	17 (51.5)	117 (46.2)	5.25	0.073
Formula feeding	4 (12.1)	10 (4)		
Mixed feeding	12 (36.4)	126 (49.8)		
History of COVID-19 exposure	4 (12.5)	25 (10.3)	0.15	0.702
Yes	28 (87.5)	218 (89.7)		
Oxygen required	33 (100)	231 (91.3)	3.11	0.078
Yes	0	22 (8.7)		

noticeable respiratory symptoms, such as rapid breathing and breathing difficulties, necessitating respiratory support such as mechanical ventilation or noninvasive ventilation with a breathing machine, as shown in Table 2. No deaths occurred among these infants.

Blood tests

The total number of white blood cells $(9.7 \pm 4.6) \times 10^9$/L in the neonates infected with COVID-19 was within the normal range. However, the total number of leukocytes in symptomatic neonates was lower than that in asymptomatic neonates (9.4 ± 4.6 vs. $11.7 \pm 4.2) \times 10^9$/L), and the absolute value of neutrophils in the symptomatic neonates was lower than that in the asymptomatic neonates (3.7 ± 2.5 vs. $6.1 \pm 3.6) \times 10^9$/L). Neonates infected with COVID-19 had significantly higher monocyte counts $(2.2 \pm 1.5) \times 10^9$/L than normal neonates. The absolute monocyte count was significantly higher in symptomatic neonates $(2.2 \pm 1.5) \times 10^9$/L than in asymptomatic neonates $(1.7 \pm 1.1) \times 10^9$/L. The percentage of monocytes was also significantly higher in the symptomatic group than in the asymptomatic group (22.8 ± 7.3 vs. $15.4 \pm 9.1) \times 10^9$/L, and the differences were statistically significant ($P < 0.05$).

The procalcitonin (PCT) level of neonates infected with COVID-19 was 0.9 ± 6.5 ng/ml, which was within the normal range. The CRP levels were normal (3.4 ± 9.7 mg/L) in the majority of patients, and only 9 patients had a significant increase in CRP levels (≥10 mg/L), suggesting the possibility of bacterial infection due to elevated levels of CRP. However, the blood culture results for these patients were negative. Myocardial enzyme CK-MB, alanine aminotransferase, aspartate aminotransferase, uric acid, urea, creatinine and other indexes in blood biochemistry were all within the normal range, as shown in Table 3.

Treatment and outcomes

A total of 286 children were admitted to the hospital after routine symptomatic treatment, and they were discharged after their condition improved. The average duration of hospitalization for neonates infected with COVID-19 was 5.6 (2.1–13) days.

In the neonatology department, some treatments were routinely given. Newborns with fever were typically managed with physical cooling methods, such as the application of ice pillows or reduction of the temperature of warm boxes. The use of drugs such as ibuprofen to lower fever in newborns was uncommon. When newborns experienced cough symptoms, they were often treated with a nebulized budesonide suspension, while oral ambroxol hydrochloride expectorant medication was recommended for newborns with phlegm. However, importantly, this treatment approach may not be considered completely standardized.

A total of 109 patients were treated with antibiotics prophylactically upon admission, the infection index became normal within 3 days, and the antibiotics were stopped after bacterial infection was excluded. No definitive evidence of bacterial infection was found in newborns with COVID-19 infection. In the study, prophylactic antibiotics were used for newborns with fever if bacterial infections could not be ruled out for some time. The commonly used drugs were ampicillin (50 mg/kg, q12h or q8h, depending on gestational age and postnatal age), piperacillin tazobactam (100 mg/kg, q12h or q8h), ceftazidime (50 mg/kg, q12h or q8h) and cefotaxime (50 mg/kg, q12h or q8h).

Some newborns and premature infants in this study were fed by nasogastric feeding due to their need for respiratory support or poor sucking ability. Once these newborns were weaned off mechanical ventilation or had developed a stronger suckling ability, the nasogastric tube was removed and replaced with self-suction.

TABLE 2 Clinical symptom, treatment and short-term outcomes.

Variables	Number of cases or days	Percentage (%)
Fever and other symptom	220	76.9
Fever only	181	63.3
Cough	34	11.9
Shortness of breath	15	5.24
Poor appetite	7	2.4
Cough with nasal congestion or runny nose	4	14.0
Poor general status	1	0.3
Oxygen need	20	7
Non-invasive ventilator	3	0.1
Invasive mechanical ventilation	1	0.3
Length of Hospital stay	5.6	-

Discussion

During the COVID-19 pandemic, numerous published studies on COVID-19 infection in children, including newborns, were conducted prior to the Omicron variant outbreak. Because they have generally low immune function, newborns are more likely to suffer from COVID-19, so they need more attention. COVID-19 has mutated several times. The Omicron variant has become widespread, and the World Health Organization has defined it as the fifth variant of concern (18, 19). In a systematic review that included all articles published from December 1, 2019, to May 12, 2020, a quarter of newborns were asymptomatic, and the rest showed typical acute respiratory infections and/or gastrointestinal symptoms. Most did not need oxygen support, their average length of hospital stay was 10 days, and their prognoses were good (20). However, there have been few reports of newborn infections during the Omicron epidemic, and the clinical characteristics and prognoses of these newborns are not very clear.

The Foshan outbreak was caused by a variant of Omicron, which infected the vast majority of the population. The clinical symptoms in children after infection are not the exact same as those in adults (21). The main manifestations in children are fever, cough, sputum, nasal congestion, runny nose, headache, diarrhoea, abdominal distension, and anorexia, and some severe patients may have convulsion (5, 22). There have been scattered reports of COVID-19 infections among newborns in China

TABLE 3 Laboratory test results.

Variables	Mean value	Standard deviation	Minimum value, Maximum value	Mean value	Standard deviation	Minimum value, Maximum value	*t*	*P*
	Asymptomatic group ($n = 33$)			Symptomatic group ($n = 253$)				
White blood cells	11.7	4.2	5.3, 19.8	9.4	4.6	3,26.1	2.77	0.010
Neutrophil count	6.1	3.6	0.8, 12.9	3.7	2.5	0.6, 15.5	4.79	<0.001
Neutrophil count %	49.8	17.6	5.8, 74.6	37.9	13.7	8, 75.1	4.54	<0.001
Monocyte	1.7	1.1	0.2, 5.8	2.2	1.5	0.2, 8.4	−1.97	0.050
Monocyte %	15.4	9.1	1.5, 36.2	22.8	7.3	2.8, 39.4	5.28	<0.001
Lymphocyte	3.6	2.2	1, 11.7	3.3	1.8	0.6, 9.7	0.99	0.320
Lymphocyte %	31.2	15.6	13.6, 83.9	36.3	14.6	9.6, 78	1.89	0.06
Red blood cell	4.6	0.6	3.2, 6.1	4.2	0.7	2.6, 7	3.4	<0.001
RBC volume distribution	55.1	9.1	16.1, 74.1	48.9	13.9	0.1, 72.2	2.49	0.010
PLT distribution	19.5	40.3	9.3, 240	16.7	38.0	8.6, 488	0.4	0.690
Average PLT volume	10.4	1.5	8.6, 15.2	11.0	1.5	7.9, 16.3	2.38	0.020
Hemoglobin	159.3	22.1	108, 209	137.7	23.4	33.7, 198	5.01	<0.001
Haematokrit	4.6	13.2	0.3, 48.5	4.4	12.4	0.3, 56.6	0.1	0.920
Mean RBC volume	99.0	7.2	76.9, 115.2	96.4	6.4	66.4, 113.4	−2.15	0.030
Platelets	281.0	90.8	108, 461	321.0	101.9	40, 658	2.15	0.030
C reactive protein	3.7	6.3	0, 29.2	3.3	10.1	0, 144.5	0.19	0.850
Procalcitonin	0.5	0.9	0.1, 3.9	0.9	6.9	0.1, 96.6	−0.28	0.780
Lactic dehydrogenase	485.7	256.0	273, 1,346	336.1	112.9	25, 1,116	4.15	<0.001
Creatine kinase	282.8	193.2	67, 828	130.7	66.8	34, 431	6.84	<0.001
Creatine kinase-MB	39.0	22.8	13.5, 110	25.4	30.9	0.3, 291	1.95	0.050
Beta-2 microglobulin	5.0	2.2	2.7, 9.9	12.7	56.5	2.5, 518	−0.45	0.650
Creatinine	44.4	19.6	11, 90	27.2	10.3	4.2, 84	7.79	<0.001
Uric acid	180.6	102.6	17, 460	161.4	58.8	34, 473	1.54	0.120
Blood urea	2.9	1.6	0.9, 8.4	3.2	2.1	0.7, 29	−0.81	0.420
Albumin	36.6	4.5	29.8, 56.5	36.9	3.0	29.9, 52.1	−0.63	0.530
Prealbumin	80.1	33.5	0.1, 139	69.0	40.3	0, 153	0.96	0.340
Alanine Aminotransferase	13.9	9.3	6, 55.9	19.0	13.0	4, 160	−2.13	0.030
Aspartate amino transferase	44.7	42.7	24.3, 233	39.5	20.7	1.7, 226	1.01	0.310
PH value	7.4	0.1	7.3, 7.5	7.4	0.1	7.3, 7.6	−1.52	0.130
Oxygen partial pressure	81.2	21.0	38.6, 109	79.7	23.4	23, 190	0.24	0.810
Pressure of carbon dioxide	31.9	6.6	21.8, 42.3	36.0	7.7	15.9, 78.7	−2.07	0.040
Lactic acid	2.7	1.4	0.8, 4.9	2.1	2.5	0.3, 30	0.89	0.370
Blood sugar	4.1	1.5	2.2, 7.6	5.2	1.3	2.8, 11.2	−2.78	0.010

Normal reference range of blood indexes: white blood cells: $15–20 \times 10^9$/L, neutrophil count: $0.6–7.5 \times 10^9$/L, monocyte: $0.15–1.56 \times 10^9$/L, lymphocyte: $2.4–9.5 \times 10^9$/L, red blood cell: $3.3–5.2 \times 10^{12}$/L, mean RBC volume: 73–104 fL, red cell distribution width: 36–49 fL, PLT distribution 9–17 fL, average PLT volume: 9–13 fL, hemoglobin: 150–220 g/L, platelets: $100–300 \times 10^{12}$/L, C reactive protein: <10 mg/L, LDH: 100–240 U/L, CK: 26–140 U/L, CK-MB: <50 U/L, beta-2 microglobulin: 1.01–2.97 mg/L, creatininer: 13–33 μmol/L, uric acid: 208–428 μmol/L, blood urea: 0.8–5.3 mmol/L, albumin: 35–55 g/L; prealbumin: 150–400 mg/L, ALT: <45 U/L, AST: <45 U/L; PO_2: 50–80 mmHg, PCO_2: 35–45 mmHg, LAC: <2.8 mmol/L, blood sugar: 2.66–7 mmol/L.

(23, 24). The data are limited, and epidemiological investigations and clinical case analyses are lacking. In contrast, in most cohort studies of neonates, mild symptoms were reported, with common symptoms including shortness of breath, respiratory distress, fever, and symptoms related to gastrointestinal disorders (10, 25). In this study, the vast majority of newborns were in the same room as their mother and were breastfed. Mothers who have been infected with COVID-19 or those who have come into contact with COVID-19 patients routinely take some protective measures. There was no clear evidence of vertical transmission, which is consistent with other research results (26).

This study found that the vast majority of neonates infected with the Omicron variant showed symptoms, which is inconsistent with previous studies suggesting that most neonates infected with COVID-19 were asymptomatic and had mild symptoms (6, 7). A total of 110 neonates were diagnosed with pneumonia, and no severe or critical cases were observed. However, it should be noted that the diagnosis of pneumonia in this study may have been too broad, and the clinical manifestations were not serious, so the prognosis was not significantly different from that of neonates infected with upper respiratory tract infection. Notably, according to the clinical manifestations, chest radiographs and CT reports, a considerable number of infected neonates were diagnosed with pneumonia, but their clinical manifestations were mild. There was no significant difference in treatment or length of stay between the two groups.

In this study, fever was the most common clinical manifestation of COVID-19 infection, which is similar to many past studies (5). This was followed by cough, shortness of breath, poor appetite, cough with nasal congestion or runny nose, and poor spirit. The clinical manifestations of symptomatic neonates were generally not severe, and the duration of symptoms was not long, which is

consistent with the reports of most previous studies (4, 5). Due to the limited long-term follow-up of these studies, current evidence cannot be used to conclude that there is no harm to neonates following infection with COVID-19. In this study, a few newborns with underlying diseases (such as persistent pulmonary hypertension, neonatal pneumonia, and malnutrition in premature infants) developed clinically unexplained severe conditions after infection with COVID-19, which resulted in a prolonged duration of severe symptoms (such as long-term mechanical ventilation, noninvasive ventilator-assisted ventilation, and oxygen inhalation) and hospital stay, but no serious complications were found in other infected children. A limitation of this study is that the diagnosis of neonatal pneumonia may have a problem with scope. In this study, the diagnosis of pneumonia was mainly based on clinical symptoms such as shortness of breath and cough plus chest radiograph or CT results because the symptoms of neonatal pneumonia are not typical.

There has not been much research on the laboratory testing of neonates infected with COVID-19, and these neonates may have normal or reduced white blood cell counts, a decreased neutrophil count that can persist for several months and/or lymphocytopenia (27–30). Previous studies have shown that newborns infected with COVID-19 have normal or decreased white blood cell counts and decreased lymphocyte levels compared with uninfected newborns (5, 6, 31). In contrast to previous studies, this study investigated the blood test results of symptomatic and asymptomatic newborns infected with COVID-19. In this study, the white blood cell counts and neutrophil levels were significantly decreased in neonates infected with COVID-19, but they were basically within the normal range, and these results were not entirely consistent with those reported in previous studies (1, 2, 5, 6). However, as previously reported, there was a significant decrease in the levels of leukocytes, neutrophils, and lymphocytes in newborns infected with COVID-19 who exhibited symptoms compared to those who were asymptomatic (29). This study had a larger patient sample size, and our research indicates that symptomatic neonates infected with the Omicron variant experience a significant decrease in the levels of neutrophils and lymphocytes.

Studies have shown that the monocyte levels of newborns infected with COVID-19 are increased (12). The proliferation of monocytes in this study was a noteworthy feature. Monocytes, a subset of white blood cells, mainly originate from myeloid progenitor cells in bone marrow, exist in the bloodstream and can differentiate into macrophages and dendritic cells (DCS) in tissues. As a result of pathological conditions, including viral infection, monocytes are activated and recruited by inflammatory mediators, migrate into affected tissues, and recruit macrophages and DC-like phenotypes. To realize the effector function of proinflammatory and anti-inflammatory activity, antigen presentation and tissue remodelling occur (32). They play an important role in host defence and excessive inflammation (19). Study results are inconsistent regarding changes in the number of monocytes in the blood during coronavirus infection. In some studies, flow cytometry analysis of blood samples from COVID-19 patients showed no change in the number of monocytes; however, the monocytes were larger than normal, which was related to the inflammatory phenotype (20). There are also studies showing that the number of monocytes in the blood of COVID-19 patients is significantly reduced (33). In the study by Andonegui-Elguera et al., the number of monocytes in the blood was increased, and the numbers of other cells, including lymphocytes, neutrophils, natural killer (NK) cells, and T cells, decreased significantly (34). In this study, it was found that the absolute value and percentage of monocytes increased significantly after COVID-19 infection, suggesting that monocytes may play an important role in neonates infected with COVID-19. Although mononucleosis is a double-edged sword, it does not cause serious cytokine storms in neonatal cases, its clinical symptoms are relatively mild, and its short-term prognosis is good.

Other indicators, such as CRP and PCT, in infected neonates were within the normal range, which was consistent with the typical characteristics of viral infection. According to previous studies, after adult infection with COVID-19, TNF-α, interleukin and other indicators have significant changes, and even some severely infected individuals have excessive inflammation and cytokine storm phenomena (34). Cytokines were not detected in this study, so further research is needed.

In previous studies, the transmission of COVID-19 was mostly horizontal, but the possibility of vertical transmission cannot be ruled out (24, 35). Maternal vaccination is a very important measure to prevent neonatal infection (36). Additionally, if the mother or other family members are infected with COVID-19, they should take protective measures, such as wearing a mask, washing their hands, and ventilating the room. Current research shows that if mothers take appropriate preventive measures, it is safe to allow newborns to be in the same room as their mothers and receive breast milk care directly (26). The main limitations of this study are the lack of information on the vaccination status of pregnant women and evidence of vertical transmission (e.g., COVID-19 status of mothers during delivery, placental examination, umbilical cord blood PCR, etc.). The other limitation of this study was the insufficient data available on maternal vaccination. This missing information could possibly provide insight into whether vaccinated mothers offer protection to their newborns.

In conclusion, newborns with COVID-19 infection caused by the omicron variant may be asymptomatic or have mild symptoms with a short duration and have a good short-term prognosis. However, long-term follow-up on physical and neurological development is still needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Affiliated Foshan

Women and Children Hospital, Southern Medical University (approval number: FSFY-MEC-2023-022). Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: This is retrospectively collected data study, and the datasets were fully anonymized prior to analysis. The need for consent was waived by the Academic Board of the Hospital.

Author contributions

Y-HD and JS designed this research and drafted the manuscript. CL, GY, WM, RH, ZW, DL, XZ, HL and LL collected the samples; JC provided help in the statistical analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Cytokine responses to SARS-COV2 infection in mother-infant dyads: a systematic review and meta-analysis

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Background: The COVID-19 pandemic has affected a significant number of pregnant women worldwide, but studies on immune responses have presented conflicting results. This study aims to systematically review cytokine profiles in pregnant women with SARS-CoV-2 infection and their infants to evaluate immune responses and potential transplacental transfer of cytokines.

Materials and methods: A comprehensive search of 4 databases was conducted to identify relevant studies. Inclusion criteria included studies measuring individual cytokines in pregnant women and/or their neonates. Studies were evaluated for quality, and data were extracted for analysis. Meta-analyses were performed using the random-effects model.

Results: Seventeen studies met the inclusion criteria, including data from 748 pregnant women and 287 infants. More than three of these studies evaluated data of 20 cytokines in maternal serum, and data of 10 cytokines was available from cord blood samples. Only the serum level of CXCL10 was significantly up-regulated in SARS-CoV-2 positive pregnant women ($n = 339$) compared to SARS-CoV-2 negative pregnant women ($n = 409$). Subset analysis of maternal samples ($n = 183$) collected during the acute phase of COVID-19 infection showed elevated CXCL10 and IFN-γ. No significant differences in cytokine levels were found between cord blood samples collected from infants born to mothers with ($n = 97$) and without ($n = 190$) COVID-19 during gestation. Subset analysis of cord blood samples collected during the acute phase of maternal infection was limited by insufficient data. The heterogeneity among the studies was substantial.

Conclusion: The findings suggest that maternal cytokines responses to SARS-CoV-2 infection during pregnancy are not significantly dysregulated, except for CXCL10 and IFN-γ during the acute phase of illness. No evidence of increased cytokine levels in cord blood samples was observed, although this could be impacted by the time period between initial maternal infection and cord blood collection. These results provide some reassurance to parents and healthcare providers but should be interpreted cautiously due to study variations and limitations.

KEYWORDS

SARS-CoV2, pregnancy, cytokines, mother-infant dyad, cord blood

Introduction

Pregnancy involves changes in the immune system of women to ensure tolerance of the fetus, which may make pregnant women more vulnerable to any infection. COVID-19 has a significant negative impact on pregnancy. Compared with non-pregnant women of a similar age, pregnant women are at a higher risk of developing severe COVID-19, requiring intensive care unit admission, mechanical ventilation or extracorporeal membrane oxygenation support, and even death (1–4). Additionally, there is an increased risk of obstetric complications and adverse birth outcomes, such as maternal hypertension and preterm birth in mothers with COVID-19 during pregnancy s (3–7).

Current data suggests that vertical transmission of the SARS-CoV-2 virus to the fetus is relatively rare (7). However, studies have provided evidence of the transplacental passage of immune mediators, including virus-specific antibodies and cytokines, in response to maternal infections, including SARS-CoV-2 (7–9). Previous research on influenza virus pandemics has demonstrated a 2–3 fold increased risk of autism spectrum disorder and schizophrenia in offspring of women who had influenza during pregnancy (10–12). Moreover, the injection of Poly I:C, a synthetic double-stranded RNA viral mimetic, in rodent models has been demonstrated to induce substantial maternal immune activation and lead to behavioral phenotypes resembling autism spectrum disorder (ASD) and Schizophrenia (13–15). This raises concerns about the long-term neurodevelopmental outcomes in children born to mothers with SARS-CoV-2 infection during pregnancy. In a global context where around 140 million live births take place each year, and with a prevalence of up to 15% of SARS-CoV-2 positivity among pregnant women in urban areas, it is estimated that as many as 20 million children could be exposed to maternal COVID-19 infection during pregnancy annually (16, 17). This situation raises significant concerns, especially in regions where pregnant populations have low COVID-19 vaccination rate. There are limited reports on the long-term neurodevelopment of children who were born to mothers with SARS-CoV-2 infection during pregnancy. An electronic health record (EHR)–based 12-month follow-up study of over 7,000 deliveries, including more than 200 COVID-19-exposed pregnancies, suggested that prenatal SARS-CoV-2 infection is associated with an increased risk of neurodevelopmental disorders in offspring (18). A prospective cohort study using a standardized observer-based assessment showed normal neurodevelopment at 5–11 months in infants born to mothers with asymptomatic or mild SARS-CoV-2 infection during pregnancy (19). Two recent meta-analyses found that gestational exposure to SARS-CoV-2 did not change overall neurodevelopment in the first year of life (20, 21) except for negative effects on fine motor and problem-solving skills (21). Large scale and longer neurodevelopment follow-up studies are needed.

There exist various plausible mechanisms through which maternal infection with SARS-CoV-2 could impact the developing fetal brain. In addition to immune factors, non-immune mediated effects could potentially impact fetal brain development, such as direct viral infection of fetal neurological cells through transmission across the placenta and compromised placental function, which can lead to adverse pregnancy outcomes and an elevated risk of neurological harm, such as fetal growth restriction, premature birth, or placental abruption. Recent investigations, involving both human subjects and animals, into the consequences of maternal immune activation resulting from viral and bacterial infections during pregnancy have underscored the role of maternal cytokines in potentially contributing to the pathogenesis of preterm birth and negative neurodevelopmental outcomes in the offspring (15, 22–24). While a few studies have examined changes in peripheral blood cytokine levels in response to acute SARS-CoV-2 infection during pregnancy (25–41), their findings are not entirely consistent, possibly due to limited sample sizes, variations in study design, or other factors that can influence cytokine levels, such as timing of sample collection, treatment of infection and inflammation. Therefore, the aim of this study is to systematically review the cytokine profiles of mothers with SARS-CoV-2 infection during pregnancy. Additionally, we will review the cord blood cytokine profiles of infants exposed to SARS-CoV-2 during gestation to evaluate the potential transplacental transfer of these cytokines.

Materials and methods

Our study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (42). In collaboration with a medical librarian, we conducted a comprehensive search of the PUBMED, EMBASE, Web of Science, and Coronavirus Research Databases to identify relevant literature published until August 2022. The search strategy is described in detail in **Supplementary File S1**. Two reviewers (SJ and EIA) independently screened the titles and abstracts of the articles identified through the search. Any disagreements regarding the inclusion or exclusion of a study were resolved through consensus, and if necessary, consultation with a third author (XP).

The following inclusion criteria were applied to select articles for this systematic review and meta-analysis: all studies that evaluated the measurement of individual cytokines in pregnant women and/or their neonates were included. For the control group, data on individual cytokine measurements from healthy pregnant women and their neonates were collected from the same selected studies. We only included studies evaluating maternal serum samples or cord blood samples. We considered studies of any design and from any period since the outbreak of SARS-COV2 commenced as eligible for inclusion. We established exclusion criteria, which entailed the removal of case reports pertaining to individual patient, literature reviews, studies involving nonhuman subjects, editorials, comments, and expert opinions from our analyses. The full texts of potentially relevant studies were carefully reviewed to determine their eligibility based

on the inclusion and exclusion criteria. The final list of included studies was identified through consensus among the reviewers.

The reviewers then independently extracted data from the included studies. The extracted details included baseline information on the study population, the number of patients in each study group, the measured immunological indicators, and the methods used for testing. These details are presented in Table 1. We focused our subsequent analysis solely on immune mediators that had been investigated in at least three included studies. Mean values (in pg/ml) of individual cytokines were extracted from the manuscript texts, tables, supplementary data, source data, and figures of each study.

Statistical analysis

We collected the number of participants, the mean and standard deviation (SD) values for immune mediators from

TABLE 1 Characteristics of included studies.

Source	Country	Study design/ patient group	Sample size		Sample assessed	Cytokines assessed	Detection method
			Study cohort	Controls			
Boelig et al. (25)	USA	Retrospective cohort study, at at Thomas Jefferson University Hospital from March 2020 to July 2021	RT-PCR confirmed COVID19 pregnant women (anytime during pregnancy), $N = 58$	Pregnant women with no signs of COVID19, $N = 142$.	Maternal serum at delivery, Cord blood and placenta	1β, IL-8, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-13, IFNg, and TNFα	Meso Scale Diagnostics platform using the 10-plex human Proinflammatory panel kit
Brancaccio et al. (26)	Italy	Prospective observational case-control study, enrolled between January 2021 and June 2021	RT-PCR confirmed COVID19 pregnant women, $N = 22$	Pregnant women with no signs of COVID19, $N = 22$	Maternal samples collected at admission to COVID maternity ward	2 cytokines- IL-6, IL-8	ELISA on maternal serum and cord blood samples for IL6, 8.
Cerbulo-Vazquez et al. (27)	Mexico	Prospective observational case-control study	RT-PCR confirmed COVID19 pregnant women, $N = 14$	Pregnant women with no signs of COVID19, $N = 13$	Maternal serum samples collected at enrollment	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, and IL-17a) and chemokines (CXCL8/IL-8, CXCL10/IP-10, CCL11/Eotaxin, CCL17/TARC, CCL2/MCP-1, CCL5/RANTES, CCL3/MIP-1a, CXCL9/MIG, CXCL5/ENA-78, CCL20/MIP-3a, CXCL1/GROa, CXCL11/I-TAC and CCL4/MIP-1b	Bead-based immunoassays (CBA kit, Cat. 560484, BD Pharmingen, San Diego, CA, USA; and LEGENDplex, Cat. 740003, BioLegend, San Diego, CA, USA, respectively
Chen et al. (28)	China	Retrospective single-center study, enrolled between Jan-April 2020	RT-PCR or specific Ab positive pregnant women, $N = 11$	Healthy pregnant women, $N = 10$	Maternal serum samples accessed from the specimen bank at Tongji Hospital, no timing specified	48 cytokines- FGFb, Eotaxin, GCSF, GM-CSF,IFNg, IL1B, IL1ra, IL1a, IL2ra, IL3, IL12 (p40), IL16, IL2, IL4, IL5, IL6, IL7, IL8, IL9, GRO-a, HGF, IFN-a2, IL10, IL12(p70), IL13, IL15, IL17a, IP10, MCP1, MIG, b-NGF, SCF, SCGFB, SDF1A, MIP1A, MIP1B, PDGF-BB, RANTES, TNFa, VEGF, CTACK, MIF, TRAIL, IL18, M-CSF, TNFB	Measured using the 152 bio-plex pro human cytokine screening panel (Bio-Rad)

(*Continued*)

TABLE 1 Continued

Source	Country	Study design/ patient group	Sample size		Sample assessed	Cytokines assessed	Detection method
Chen et al. (29)	China	Retrospective single-center study, enrolled between Jan-May 2020	RT-PCR or specific Ab positive pregnant women, $N = 16$, 4 for IFN	Healthy pregnant women, $N = 4$	Maternal serum samples accessed from the specimen bank at Tongji Hospital, between 56 and 119 days after the symptom onset	IL-6, IL-1b, IL-2R, IL-8, IL-10, and TNF-α	ECLIA (electrochemiluminescence immunoassay) Roche Diagnostics, DiaSorin
DeBiasi et al. (30)	Italy	Case- control, cross-sectional, single-center study	RT-PCR confirmed COVID19 pregnant women, $N = 14$	RT-PCR negative healthy, age matched pregnant women, $N = 28$	Maternal serum samples obtained at enrollment	62 cytokines- G-CSF, PDGF-AA, EGF, PDGF-AB/BB, VEGF, GM-CSF, FGF, GRZB, IL- 1A, IL-1RA, IL-2, IL-27, IL-4, IL-6, IL-10, IL-13, TNF, IL-17C, IL-11, IL-18, IL-23, IL-6RA, IL-19, IFN-B, IL-3, IL-5, IL-7, IL-12p70, IL-15, IL-33, TGF-B, IFN-G, IL-1B, IL-17, IL-17E, CCL3, CCL11, CCL20, CXCCL1, CXCL2, CCL5, CCL2, CCL4, CCL19, CXCL1, CXCL10, PD-L1, FLT-3, TACI, FAS, LEPTIN R, APRIL, OPN, BAFF, LEPTIN, BMP4, CD40 LIGAND, FAS LIGAND, BMP7, BMP2, and TRAIL	Luminex platform (Human Cytokine Discovery, R&D System, Minneapolis, MN
Febryanna et al. (31)	Indonesia	Case- control, cross-sectional, single-center study	RT-PCR confirmed COVID19 pregnant women, $N = 25$	RT-PCR negative healthy, pregnant women, $N = 25$	Maternal serum sample collected at admission for delivery	TNF-a	BD CBA (cytometric bead array) human Th1/Th2 Cytokinekit II CAT No. 551809
Garcia-Flores et al. (32)	USA	Case- control, cross-sectional, single-center study	RT-PCR confirmed COVID19 pregnant women, $N = 12$. 8 asymptomatic, 1 mild symptoms and 3 severe COVID-19 (requiring O2)	RT-PCR negative healthy, pregnant women, $N = 11$	Maternal blood samples were collected upon admission, mostly all term gestation and cord blood at delivery	20 cytokines- IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNFA (Pro-inflammatory Panel 1) or GM-CSF, IL-1α, IL-5, IL-7, IL-12/IL- 23p40, IL-15, IL-16, IL-17A, TNF-β, and VEGF-A	V-PLEX Pro-Inflammatory Panel 1 (human) and Cytokine Panel 1 (human) immunoassays (Meso Scale Discovery, Rockville, MD, USA)
Gee et al. (33)	UK	Case- control, cross-sectional, single-center study, May 2020-March 2021	RT-PCR confirmed COVID19 pregnant women, R/O (Infection within 2 weeks of delivery) $N = 15$, Recovered (nfection in early gestation) $n = 14$	RT-PCR negative throughout pregnancy, healthy, pregnant women, $n = 15$	Umbilical cord blood samples and paired maternal blood samples collected at the time of delivery	13 cytokines- IL-1β, IL-6, TNF, IP-10, CXCL8, IL-12p70, IFN-α2, IFN-λ1, IFN-λ2/3, GM-CSF, IFN-β, IL-10 and IFN-γ	13-plex LegendPlex human anti-virus response panel kit (BioLegend)
Rosen et al. (34)	USA	Observational study, single center, cross sectional study, March-April 2020	RT-PCR confirmed COVID19 in pregnant women at admission during 3rd trimester, $n = 44$	RT-PCR negative healthy, pregnant women in 3rd trimester, $n = 25$	Maternal blood samples drawn at admission for symptoms or delivery	7 cytokines- G-CSF, HGF, IL-18, IL-1Ra, IL-2Ra, IL-8, and IP-10	Quantikine ELISA kits from R&D Systems (Minneapolis, MN, USA)

(*Continued*)

TABLE 1 Continued

Source	Country	Study design/ patient group	Sample size		Sample assessed	Cytokines assessed	Detection method
Taglauer et al. (35)	USA	Prospective cohort study from July 2020 through June 2021	RT-PCR confirmed COVID19 anytime during pregnancy, $N = 31$	Contemporary RT-PCR negative healthy, pregnant women, $N = 29$	Maternal blood and cord blood/infant blood at the time of delivery	13 cytokines- IP-10, IL-1β, IL-6, TNF-α, IFN-λ1, IL-8, IL-12p70, IFN- α2, IFN-λ 2/3, GM-CSF, IFN- β, IL-10, and IFN-γ.	LEGENDplex assay (BioLegend)
Tanacan et al. (36)	Turkey	Prospective case-control study	Pregnant women with confirmed COVID-19 infection, $N = 90$	Gestational age-matched control group of healthy pregnant women, $N = 90$	Blood samples were collected from the participants along with the initial laboratory tests upon their first admission to the hospital.	5 cytokines- IFN γ, IL-2, IL-6, IL-10, and IL-17	ELISA kits by eBioscience, Thermo Fisher Scientific
Tartaglia et al. (37)	Italy	Prospective case-control study	COVID recovered Pregnant women (pCOV), $n = 17$	COVID recovered matched non-pregnant women (nCOV), $n = 12$	Maternal serum samples, no timing mentioned	11 cytokines, chemokines, and growth factors- GM-CSF, IFN-gamma, IL-1 beta/ IL-1F2, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 p70, IL-13, TNF-alpha, IL-17	Luminex Human Th1/Th2 11-plex Fixed Panel, Human IL-17 immunoassay, biotechne
Gonzalez-Mesa et al. (38)	Spain	Observational and prospective study, November 2020 to May 2021	RT-PCR confirmed COVID19 in pregnant women during labour or anytime during pregnancy, $n = 79$	None	Blood samples were collected from the mother at the time of labor and from the umbilical cord immediately after birth	3 cytokines- IL1b, IL6, and IFN-γ	ELISA
Briana et al. (39)	Greece	Prospective, observational study March 2020 and April 2021	Term infants born to previously healthy mothers; uncomplicated up to term pregnancies; positive for SARS-CoV-2 maternal nasopharyngeal swabs at delivery, negative neonatal RT-PCR, $N = 40$	None	Neonatal blood on Day 0	1 cytokine- IL6	ELISA
Liu et al. (40)	China	Prospective, observational study January 20 to March 3, 2020	Term newborns born to mothers with RT-PCR pos COVID-19, $N = 51$	None	Blood samples were collected within 3 days after birth for the detection of immunoglobulin levels, cytokine concentrations, and lymphocyte subsets.	6 cytokines- IFN-g, IL-2, IL-4, IL-6, IL-10, and TNF-a	FACS Calibur Flow Cytometer (BD Biosciences)
Zhong et al. (41)	China	Retrospective, observational study	RT-PCR confirmed COVID19 pregnant women, $N = 36$	RT-PCR negative pregnant women, $N = 36$ (No cytokines)	Blood sample collected at admission for delivery or illness	IL4, IL6, IL10, TNFa, IFNg	Flow Cytometry (CellGene Biotech Co)

serum samples of pregnant women with and without COVID-19, as well as from cord blood samples of infants born to mothers with and without COVID-19 during pregnancy. We conducted a subset analysis of maternal serum samples collected within 2 weeks of COVID-19 diagnosis to capture acute and ongoing infection. COVID-19 infection was confirmed through a positive nasopharyngeal RT-PCR test result at any time during pregnancy in all studies. The control cohort comprised women with documented negative COVID-19 nasal swabs throughout their pregnancy. Women who received the COVID-19 vaccine were excluded from both the study and control cohorts. In cases where mean and SD data were not directly reported, we applied a previously established method to convert median and interquartile range (IQR) values to mean and SD. For articles presenting immunological signatures in figures, we extracted data by measuring the pixel positions of the electronic figures

and calculating the actual values. For box plots, medians and ranges were used to derive means and SDs, while scatter plots provided individual values for the computation of means and SDs.

Random effects meta-analyses were performed for all immune mediators separately for mothers and infants and for subgroups. Forest plots were generated to illustrate the differences between the two groups. Due to potential variations in cytokine testing methods across studies, which can affect the pooling of means and differences for effect estimation, we calculated a dimensionless effect measure from each study for pooling purposes. The standardized mean difference (SMD) was computed using the means and SDs and used as the effect size. Heterogeneity was assessed using the I^2 statistic. Publication bias was assessed using funnel plots and the Begg and Egger tests. All analyses were performed in Stata v.17.1 (StataCorp, College Station, TX).

Results

A detailed flow diagram illustrating the study selection process and the number of studies selected is presented in **Figure 1**. Our literature search identified 3,235 reports up until 29 August 2022. After removing duplicates, we screened the titles and abstracts of the remaining 2,074 articles, further excluding 1,809 reports. Full texts of the remaining 263 potentially relevant studies were retrieved and evaluated for eligibility, leading to the exclusion of 246 studies from the meta-analysis for various reasons (detailed in **Figure 1**). Ultimately, 17 studies were included in the qualitative synthesis and collated for the meta-analysis (25–41). These studies were conducted in China (4), the United States (4), Italy (2), Greece (1), Indonesia (1), Mexico (1), Spain (1), and Turkey (1) (**Table 1**). All included studies reported individual cytokine levels in maternal and/or cord blood samples from pregnant individuals with and without COVID-19 infection and their infants, respectively.

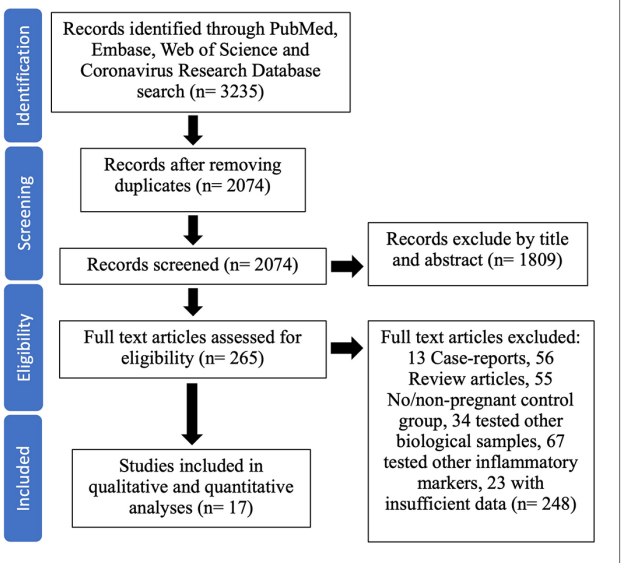

FIGURE 1
Flow diagram of the inclusion criteria for the study selection process.

The articles included data from 748 pregnant women, with 46% ($n = 339$) documented to have COVID-19 infection during pregnancy and 54% ($n = 409$) without documented COVID-19 infection. In all included reports, the study and control cohorts were matched for maternal age. The studies also included data from 287 infants, with 34% ($n = 97$) born to mothers with COVID-19 infection during pregnancy and 66% ($n = 190$) born to mothers without COVID-19 infection. More than three of these studies evaluated data on 20 cytokines in maternal serum, and data on 10 cytokines was available from cord blood samples. A comprehensive overview of the characteristics of the included studies for each immune mediator including baseline information, number of patients in each study group, measured immunological indicators and their outcome reporting measures, were extracted and summarized in **Supplementary Table S1** for maternal samples and **Supplementary Table S2** for cord blood samples.

In the subset analysis of maternal samples, only studies that reported cytokine levels during the acute phase of COVID-19 infection (i.e., sample collection and testing within 2 weeks of a documented positive nasal swab) were included. This subset analysis included data on 10 cytokines from maternal serum of 183 pregnant women with active COVID-19 infection and 214 pregnant women without COVID-19 infection. The study and control groups were age matched in all the included studies in the subset analysis as well. However, only 1 report (Tanacan et al) (36) had gestational age matched study and control cohorts from every trimester. It is important to note that 4 reports (26, 27, 32, 34) out of the remaining six (26, 27, 30, 32, 34, 35) in the subset analysis, primarily enrolled women with COVID 19 positive nasopharyngeal swab closer to delivery and thus the mean gestational age between the study and control groups were similar (~38–39 weeks of gestation) in these studies. Similar details were extracted and summarized in **Supplementary Table S3** for each study in the subset analysis. For these studies, only measurements acquired during the acute phase of infection were used for the analysis. **Supplementary Table S3** provides an overview of the characteristics of the included studies for each immune mediator in the subset analysis.

When comparing COVID-19 positive pregnant women to COVID-19 negative pregnant women, we found that only the serum level of CXCL10 was significantly up-regulated in the COVID-19 positive group (**Figure 2**). The I^2 statistic for majority of the cytokines was >95%, indicating significant heterogeneity among the studies. In the subset analysis, which included serum samples from COVID-19 positive women during the acute phase of illness, significant heterogeneity was also observed for most cytokines, except for IFN-γ, IL-1β, and IL-17 (**Figure 3**). In the subset of pregnant women with active COVID-19 during sample collection, CXCL-10 and IFN-γ were found to be significantly elevated compared to COVID-19 negative pregnant women. Finally, in the evaluation of cord blood samples, no cytokines

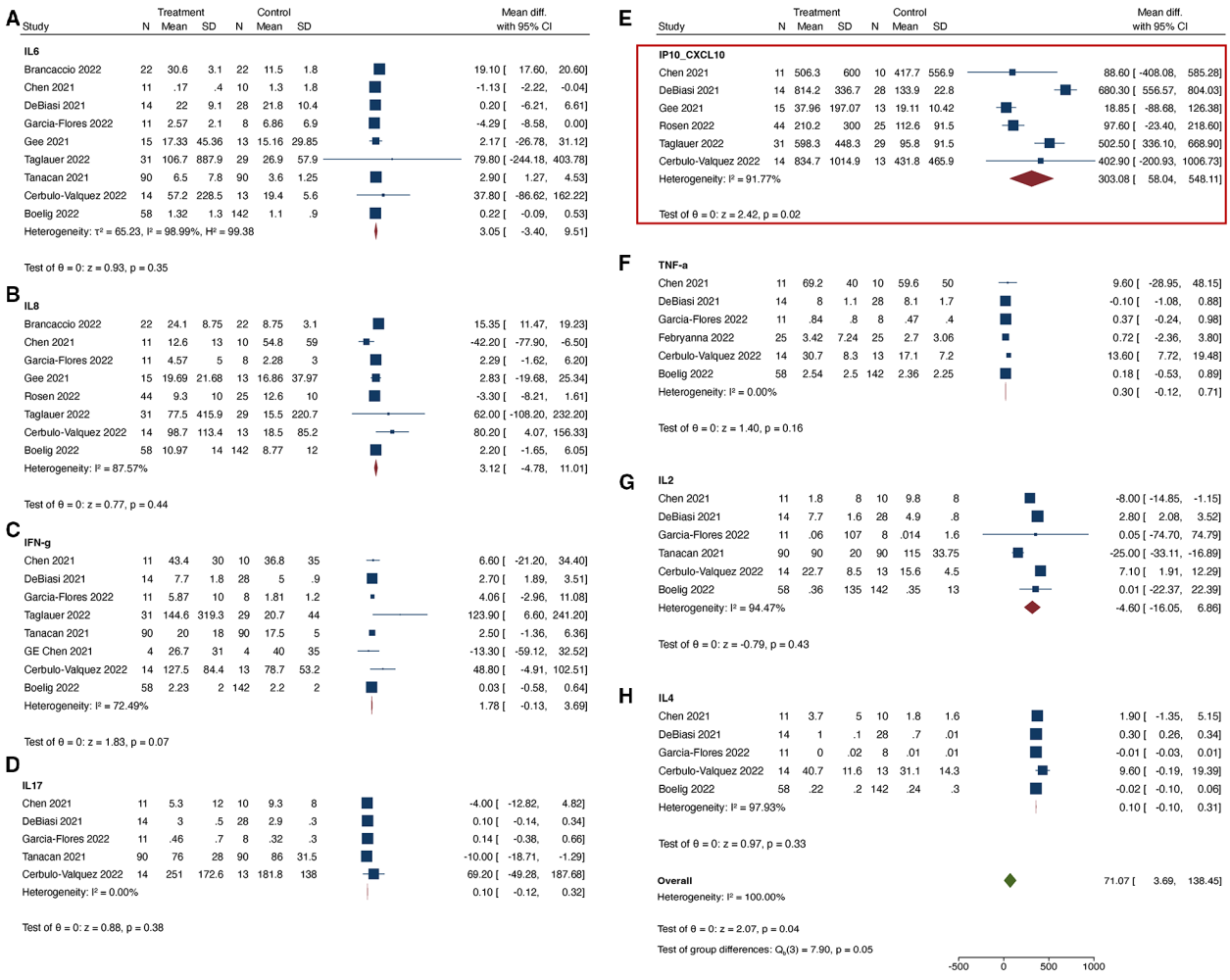

FIGURE 2
(A–H) Cytokines tested in maternal serum samples. In Figures 2–4, "Treatment" group refers to "COVID positive" and "Control" group refers to "COVID negative" pregnant individuals. All cytokines have been reported as mean values in pg/ml.

were found to be significantly elevated in infants born to mothers with COVID-19 infection during pregnancy compared to infants born to COVID-19 negative mothers (**Figure 4**). There was inadequate data to conduct a subset-analysis for the cord blood samples. The 2 studies (32, 35) that reported cytokine levels in cord blood samples collected during the acute phase of maternal COVID-19 infection showed no statistically significant increase in any cytokine levels.

Discussion

Dysregulation of the maternal immune system during pregnancy have been associated with negative pregnancy outcomes, including miscarriage, impaired fetal growth, and premature birth, which could have lasting impacts on the health of the newborns (43, 44). Amidst the COVID-19 pandemic, research has indicated elevated occurrences of preterm birth, preeclampsia, stillbirth, heightened maternal anxiety, and increased maternal mortality subsequent to SARS-CoV-2 infection during pregnancy (3–7, 45). It has been hypothesized that immune system dysregulation resulting from SARS-CoV-2 infection may mediate the observed adverse pregnancy outcomes (46). However, our meta-analysis of cytokine levels in pregnant women with and without COVID-19 infection during gestation did not demonstrate evidence of an exacerbated cytokines response in mothers with gestational COVID-19, except for elevated levels of CXCL10 and IFN-γ during the acute phase of illness. Furthermore, we found no evidence of increased cytokine levels in cord blood samples from infants exposed to COVID-19 prenatally. These findings may offer some reassurance to parents and healthcare providers caring for children born during the COVID-19 pandemic.

Systematic reviews of immune signatures secondary to COVID-19 infection in the general population have consistently reported significant elevation of cytokines like IL-6 and TNFa in severe cases (47–49). In our systematic review, we identified three studies that analyzed cytokine concentrations based on

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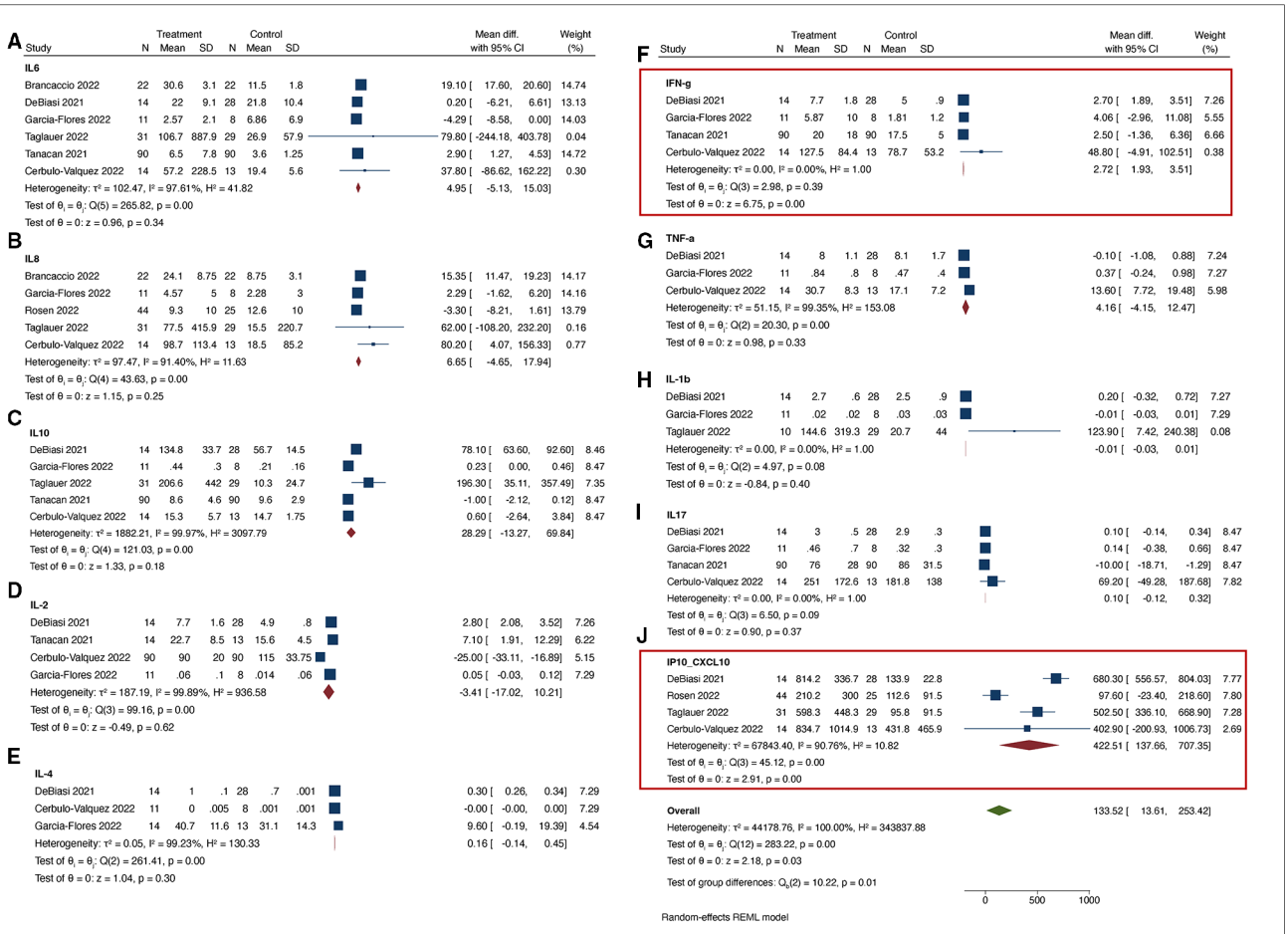

FIGURE 3
(A–J) Cytokines tested in maternal serum samples during acute phase of illness.

disease severity in the context of COVID-19 during pregnancy. However, none of these studies reported consistent cytokine profiles across all severity levels, preventing us from conducting a subset analysis by disease severity. Specifically, the studies by Garcia-Flores et al. (32) did not find a strong association between cytokine changes and disease severity in maternal or cord blood samples. In contrast, DB Rosen et al. (34) found that higher cytokine levels, including IL-18, IL-1Ra, IP-10, IL-2Ra were associated with more severe disease based on the NIH clinical spectrum. Tanacan et al. (36) reported statistically significant positive correlations between IFN γ and IL-6 with disease severity but observed a negative correlation for IL-2 and IL-10. These findings underscore the complexity of the relationship between cytokine profiles and disease severity in pregnant individuals with COVID-19 and emphasize the need to consider disease severity as an important variable in future studies.

Another factor impacting the measured cytokine levels is the timing of sample collection in relation to active infection. Our results did show an elevation of maternal serum levels of CXCL10 and IFN-γ during the acute phase of COVID-19 infection. CXCL10, a chemokine involved in immune cell recruitment, and IFN-γ, a pro-inflammatory cytokine, play pivotal roles in orchestrating the body's defense against viral infections. However, exaggerated immune responses may disrupt the intra-uterine environment during critical periods of development, posing potential complications for the fetus. Thus, the timing of infection during pregnancy may drive the eventual fetal outcomes. Longitudinal studies tracking these serum levels across the course of infection, as well as larger cohorts assessing the correlation between timing of COVID-19 infection during pregnancy, as well as disease severity with maternal-fetal outcomes, can provide deeper insights.

While the overall results of this meta-analysis are reassuring, they should be interpreted with caution. The included studies exhibited significant variation in terms of the timing of sample collection in relation to the onset of infection and the methods used to measure cytokine levels. Studies comparing available cytokine panels have demonstrated substantial variability in the sensitivity and specificity of these panels for detecting serum cytokine levels (50–52). Additionally, factors such as disease severity, treatment implementation, and pre-existing conditions were not adjusted for or evaluated. Moreover, it is important to note that cytokines represent only a portion of maternal

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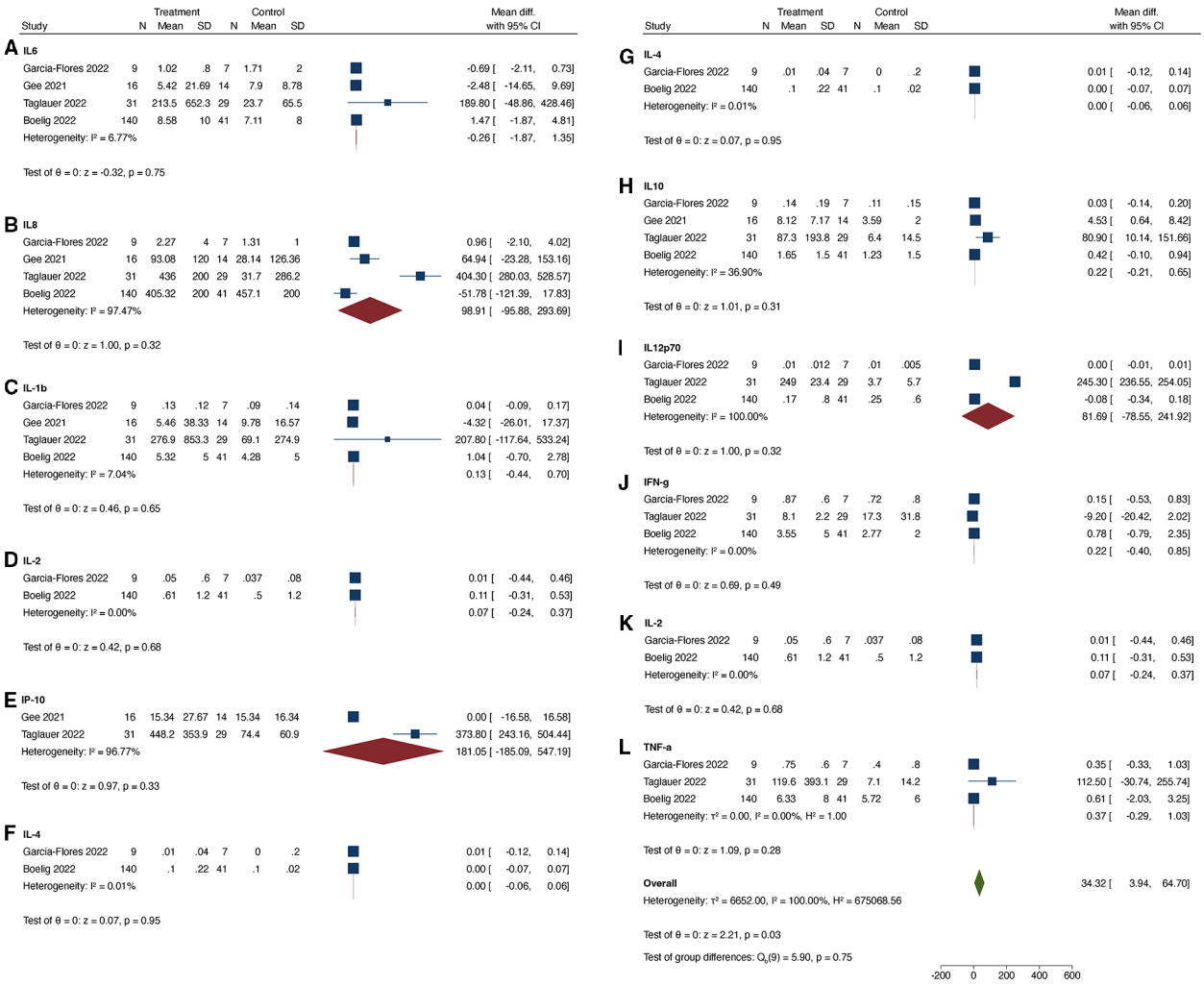

FIGURE 4
(A–L) Cytokines tested in cord blood samples.

immunology, and other immune markers play a crucial role in understanding the impact of SARS-CoV-2 infection on the maternal immune system. Therefore, despite our findings suggesting that SARS-CoV-2 infection during pregnancy does not result in exaggerated cytokines changes in mothers and infants, further studies are necessary to fully comprehend the risks associated with SARS-CoV-2 infection in pregnant mothers and offspring. The heterogeneity observed in this analysis underscores the need for more reliable and reproducible methods for testing serum cytokine levels, both for research and clinical purposes. Finally, it is imperative to conduct prospective investigations that involve ongoing evaluations throughout pregnancy. These studies should encompass diverse groups, considering various levels of SARS-CoV-2 disease severity and vaccination status. Such research is essential for advancing our comprehension of the connection between SARS-CoV-2 infection during pregnancy, alterations in maternal cytokines, and their enduring consequences on fetal development.

Conclusion

This systematic review and meta-analysis of cytokine levels shows no evidence of an exacerbated or dysregulated cytokines response to SARS-CoV-2 infection in the pregnant mothers and their newborns. However, it is important to acknowledge both the strengths and limitations of this review and meta-analysis, considering the rapidly evolving nature of the literature in this field. On one hand, our study results can provide reassurance to pregnant individuals and healthcare providers caring for infants born during the COVID-19 pandemic. On the other hand, it is crucial to emphasize that our analyses should be regarded as hypothesis-generating rather than hypothesis-testing. Further research is needed to corroborate these findings and provide a more comprehensive understanding of the immune response during pregnancy in the context of SARS-CoV-2 infection. Continued monitoring and investigation of immune markers and their impact on pregnancy outcomes are warranted to inform

clinical decision-making and optimize care for pregnant individuals and their infants.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

SJ: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. IA: Data curation, Formal Analysis, Methodology, Writing – review & editing. DS: Conceptualization, Supervision, Writing – review & editing. XP: Conceptualization, Data curation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1277697/full#supplementary-material

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Febrile seizure in children with COVID-19 during the Omicron wave

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Objective: To explore the clinical characteristics and prognosis of febrile seizure in children with COVID-19.
Methods: This study is a single-center retrospective cohort study. The cases included febrile seizures in children with COVID-19 admitted to the Renji Hospital from April 7th, 2022 to June 2nd, 2022. We compared children with and without febrile seizures in their clinical characteristics such as sex, age, symptoms, seizure manifestation, COVID-19 severity, and SARS-CoV-2 nucleic acid test results. The children with febrile seizures were followed up by telephone and outpatient service about one month after the nucleic acid turned negative and discharged from the hospital.
Results: A total of 585 cases of children with COVID-19 were included in the analysis. There were 15 children (1.8%) with febrile seizures, age from six months to three years old, nine boys (60.0%) and six girls (40.0%). The manifestations of febrile seizures were all generalized tonic-clonic seizures. The median nucleic acid negative conversion time was 11 (IQR:10.75,13) days. Our first comparison involved comparing children without underlying diseases; there was no significant difference in sex, COVID-19 severity, and clinical manifestations, but there was an age difference (2 vs. 1.3, $P = 0.047$). There was no difference in SARS-CoV-2 nucleic acid negative time between the two groups (11d vs. 13d, $P = 0.128$). One child had new clinical manifestations during the follow-up, but his EEG and MRI were normal.
Conclusion: Febrile seizure may be children's primary neurological manifestation of COVID-19. It may occur in children with no history of epilepsy and is not associated with severe illness. The long-term neurological outcomes of these children should be followed up.

KEYWORDS

febrile seizures, COVID-19, Omicron, children, febrile convulsions

1. Introduction

Children with COVID-19 account for about 10% of all COVID-19 cases and have a less severe illness compared with adult patients (1). The most common symptoms are fever and cough and other symptoms include fatigue, myalgia, nausea and vomiting, abdominal pain, and diarrhea. Most of the symptoms resolve within one week (2, 3). Neurological symptoms varied between new onset seizures, anosmia, ageusia and focal arteriopathy in many studies (4–6). During the Omicron strain epidemic, the number of COVID-19 infections, hospitalization and neurological symptoms were higher than other SARS-CoV-2 variant outbreaks (7, 8). Encephalitis and death have been reported in COVID-19 infected

children in Hong Kong, Japan, Taiwan and other regions (9). Seizure in children with COVID-19 may be caused by viral encephalitis and brain injury.

This study evaluated 585 cases of 0–3 year old young children who were hospitalized for symptomatic COVID-19 infection during the Omicron strain epidemic in Shanghai, China. We identified 15 children who developed febrile and summarized their clinical characteristics in order to provide a reference for the diagnosis and treatment of seizure in children with COVID-19.

2. Method

2.1. Study design and participants

This single-center retrospective study was conducted at Renji Hospital (South branch), School of Medicine, Shanghai Jiao Tong University, from April 7, 2022, to June 2, 2022. The hospital was designated treatment of children with COVID-19 infection during the COVID-19 pandemic in Shanghai, China. This study was approved by the ethics committee of the Children's Hospital of Fudan University (IRB No. 2022–82).

Children of age 0–3 years who had symptomatic COVID-19 infection and without underlying chronic diseases were included in the study. The study patients were divided into two groups: COVID-19 children who had febrile seizures and COVID-19 children who did not have febrile seizure during the course of infection. The disease severity of COVID-19 infection children was classified based on the WHO COVID-19 Clinical Progression Scale (9), including five categories: uninfected, mild, moderate, severe, or death.

2.2. Data collection

Demographic and clinical data of including gender, age, PCR test, infection severity, vaccination status (no data in **Table 1**), and nucleic acid test negative conversion time, were collected by reviewing the hospital electronic medical records.

2.3. Laboratory analysis

All cases were laboratory-confirmed as infected with the Omicron variant of SARS-COV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) nucleic acid test. Nasal swabs were conducted by trained nurses using a standard procedure. Specimens underwent RT-PCR tests for SARS-CoV-2 nucleocapsid gene targets with standardized methods and interpretive criteria. Two SARS-CoV-2 genes, including ORF1ab, and N were detected using SARS-CoV-2 nucleic acid detection, with a cycle threshold of <35 as a positive result, following the manufacturer's instructions.

2.4. The definition of nucleic acid conversion

The nucleic acid conversion was defined as two consecutive daily negative SARS-CoV2 PCR results. Nucleic acid conversion time was defined as the time duration from the onset of symptoms to the first time of the two (first negative day) consecutive negative PCR tests.

2.5. Follow-up

The cutoff point of follow-up was about one month (4–5 weeks) after negative PCR test and the patient was discharged from the hospital. Telephone follow-up: whether there were still COVID-19-related clinical manifestations after discharge, the time and duration of these symptoms, and whether appetite, body weight, sleep and energy changed after discharge.

2.6. Statistical analysis

The study used Microsoft Access 13.0 to create the database and SPSS 20.0 for statistical analysis. The inter-group comparisons of clinical characteristics in the seizure and the non-seizure groups were conducted by chi-square and rank-sum tests.

3. Results

During the study period, a total of 871 children were admitted to Renji Hospital for treatment of symptomatic COVID-19. Of these, 585 children age 0–3 years who did not have underlying diseases were included in the study. Patient demographic and clinical presentations are summarized in **Table 1**.

3.1. Clinical presentations of children with seizure during COVID-19 infection

There were 15 children, 9 boys and 6 girls, had febrile seizure during the course of infection (**Table 1**). They were 6 months to 3 years old, with a median age of 2 years (IQR:1.3,2.7). Seven (47%) had mild infection and eight (53%) had moderate infection. All 15 children had fever during the infection. The fevers lasted 2–4 days with peak temperatures of 38–40°C. Other symptoms included cough ($n = 9$, 60%), runny nose ($n = 4$, 27%), fatigue ($n = 3$, 20%), vomiting ($n = 1$, 7%), no diarrhea and other infection in the course of infection. All 15 children had 1–2 min generalized tonic-clonic seizures while febrile. All of them had only one seizure episode and none of them were treated antiepileptic medication. The median time of nucleic acid negative conversion in the 15 children was 11 (IQR:10.75, 13) days (**Figure 1**).

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TABLE 1 General data, clinical manifestations and telephone follow-up of children with febrile seizure.

	Gender	Age	Severity of illness	Nucleic acid conversion time (day)	Past history	Vaccination	COVID-19 related symptoms	Convulsive form	Telephone follow-up
1	Male	1 year 6 months	Mild	14	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
2	Male	2 years	Mild	11	There was one febrile seizure at the age of 1 years and 1 years 10 months.	N	Fever, Fatigue	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
3	Female	1 year 3 months	Mild	13	N	N	Fever, Cough, Fatigue	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
4	Male	3 years	Moderate	9	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
5	Male	3 years	Moderate	10	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
6	Male	8 months	Moderate	15	N	N	Fever, Cough	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
7	Female	3 years	Moderate	8	N	N	Fever, Cough, Diarrhea	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
8	Male	2 years	Moderate	13	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
9	Male	5 months	Moderate	11	N	N	Fever, Cough	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
10	Male	1 years 4 months	Moderate	12	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	There is a significant increase in night terrors/nocturnal crying.
11	Female	2 years	Mild	11	N	N	Fever, Cough	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
12	Male	2 years 8 months	Mild	11	N	N	Fever, Cough	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
13	Female	1 years 10 months	Mild	15	N	N	Fever, Cough	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
14	Female	2 years 3 months	Mild	9	N	N	Fever, Fatigue	Fever during seizures, 1 general seizure lasting 1–2 min	Normal
15	Female	2 years 5 months	Moderate	12	N	N	Fever	Fever during seizures, 1 general seizure lasting 1–2 min	Normal

3.2. Comparison between children with and without febrile seizure during COVID-19 infection

Demographics and clinical presentations of children in the seizure group and non-seizure group were compared (Table 2). There was no significant difference in sex, number of patients in different categories of infection severity and clinical manifestation between the two groups. However, there was a significant difference in median age (2 vs. 1.3 years, $P = 0.047$). There was no significant difference in nucleic acid negative conversion time between the two groups (11d vs. 13d, $P = 0.128$) (Figure 1).

3.3. Follow-up

The parents of 15 children with febrile seizures were followed up by telephone at about one month (4–5 weeks) after negative PCR test. Fourteen children (93%) were reported healthy with no persistent or new COVID symptoms or other health problems after discharge. During the telephone follow-up, the parents of Child #10 (in Table 1) reported that the child had significant increase in numbers of night terrors/crying at night but no seizures, fever, cough, gastrointestinal abnormalities and other symptoms. Two months after discharge, this child was readmitted to our hospital for

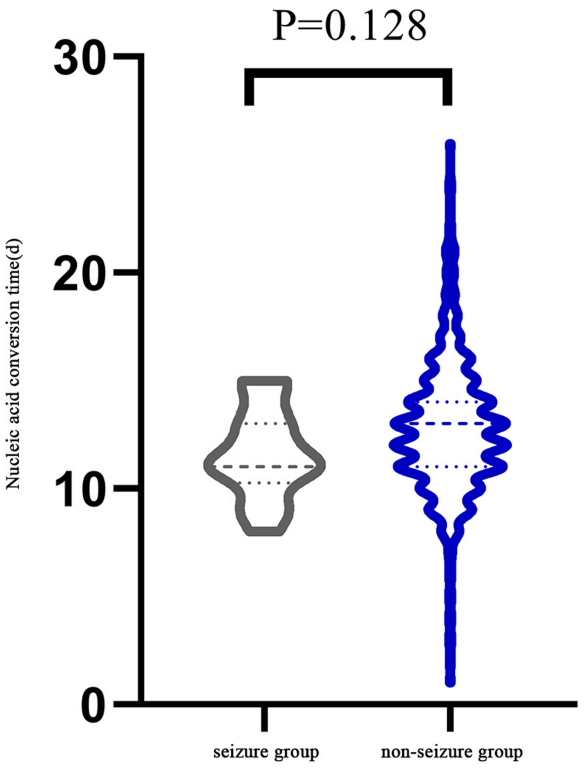

FIGURE 1
Comparison of the time required for each group since the onset of symptoms or the first positive nucleic acid.

TABLE 2 Comparison of clinical characteristics between febrile seizure group and non-febrile seizure group.

	Febrile seizure group ($N = 15$)	Non-febrile seizure group ($N = 570$)	P
Gender (%)			
Male	9 (60.0%)	328 (57.5%)	0.692
Female	6 (40.0%)	242 (42.5%)	0.692
Median age (IQR, year)	2 (1.3, 2.7)	1.3 (0.75, 2)	0.047
Severity of illness (%)			
Mild	7 (46.7%)	353 (61.9%)	0.141
Moderate	8 (53.3%)	217 (38.1%)	0.141
Severe	0 (0%)	0 (0%)	1
General symptoms (%)			
Fever	15 (100%)	540 (94.7%)	1
Cough	8 (53.3%)	319 (56.0%)	1
Diarrhea	0 (0%)	77 (13.5%)	0.248
Vomit	1 (6.7%)	61 (10.7%)	1
Fatigue	3 (20.0%)	96 (16.8%)	0.741

neurological evaluation. No abnormalities were seen on the video EEG and brain MRI.

4. Discussion

Febrile seizure is one of the most common neurological disease in infants and young children, which usually occurs from 6 months to 5 years old, and the incidence rate is 2% and 4% in children under five years old. The prognosis is usually good, although about 1/3 of children are at risk of recurrence (10). The pathogenesis of febrile seizure is not clear and is generally believed to be caused by multiple factors, including, but not limited to, elevated body temperature, viral infection, some vaccinations, family inheritance, etc. al (11). Viral infections, especially those that cause high fever, have been shown to increase neuronal excitability and lower seizure threshold, especially in the immature nervous system (12). Common viruses that cause febrile seizure include human herpesvirus 6, influenza, adenovirus, parainfluenza and chickenpox (13).

We here report 15 cases of novel coronavirus Omicron variant infection with febrile seizure in children, accounting for 1.8% of the children's cases treated in designated hospitals. A US study showed that 0.5% of children with COVID-19 were diagnosed with febrile seizure, and most of them had no co-infection, with about 9 percent of them requiring intensive care (14). In an Italian multicenter study, Garazzino et al. evaluated 168 children with COVID-19 and reported the prevalence of afebrile and febrile seizures to be 1.8% and 1.2% (3). During 2019.01–2020.12, there were 29,825 cases of febrile children without COVID-19 treated in Shanghai with a sex ratio of 1.4 (17,377 males and 12,448 females). The age ranged from 5 months to 12 years old, with an average of (5.02 ± 1.64) years. Febrile seizure occurred in 252 cases, and the incidence of febrile seizure was 0.84%. We compared our febrile seizure group with children with febrile seizure without COVID-19 in Shanghai, there were no significant differences in incidence (1.8% vs. 1.2%, $P = 0.095$) and gender ($P = 0.783$) between the two age-matched groups (15). These findings suggest that febrile seizure is not a common neurological manifestation of COVID-19 infection (14). In another study, the number of children admitted to emergency departments for febrile seizure was significantly lower than in previous years due to the habit of wearing masks and social isolation during the COVID-19 epidemic (16).

The age range of 15 coronavirus Omicron variant infection children were from 6 months to 3 years old, which conformed to the typical age range of febrile seizure, and all the seizure were generalized (tonic-clonic) seizure. Fifteen children had only one seizure in the course of the disease, and the duration was 1–2 min, which was consistent with simple febrile seizure.

Some cases have been reported in South Africa and Sweden in children outside the typical age range for febrile seizure (17, 18).

Available evidence indicates that novel coronavirus is known to be neuroinvasive and can cause cytokine storms, increasing nerve excitability (19, 20). It has also been suggested that children with COVID-19 may experience hypoxia, metabolic disorders, organ failure or brain damage, all of which may lead to a lower seizure threshold (21) in children with COVID-19, the underlying causes of seizure may be related to fever, encephalitis or childhood multiple system inflammatory syndrome (MIS-C), so we should be careful to diagnose febrile seizure. Considering the seriousness

of children infected with COVID-19, these causes must be considered when children develop seizure.

During the follow-up, one child had new health problems, and there was no abnormality in VEEG and cerebral MRI during the follow-up. Among the reported cases, the short-term outcome of nervous system injury in most children is good, but whether there are long-term sequelae remains to be further studied. A large amount of evidence shows that the incidence of post-COVID-19 syndrome is higher in adults (22), but there are few related studies in children. Therefore, it is necessary to follow up those COVID-19 cases for a longer time and the ongoing (uncompleted data) follow up program will give us more evidence.

As a retrospective single-center study, the characteristics of COVID-19 children with febrile seizure were reported for the first time in mainland China. However, due to the low incidence of febrile seizure, the overall number of cases is small.

Based on the existing 15 cases of children, we found that the clinical manifestations of febrile seizure caused by novel coronavirus were similar to those caused by other related viruses, compared with children without febrile seizure without underlying diseases in the same age group. There was no significant difference in sex, classification, clinical manifestation and viral nucleic acid negative time, and the prognosis was good. Compared with adults, febrile seizure may be the main manifestation of COVID-19 in some children. It may occur even in children who have no history of epilepsy and are not associated with serious illness. Attention should be paid to early identification and timely improvement of the relevant nervous system examination and long-term continuous follow-up to verify the impacts on the developing nervous system.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

LW and WZ: designed the project. PX: wrote the first draft and reviewed data from online databases. JZ and XC: edited subsequent drafts of the paper and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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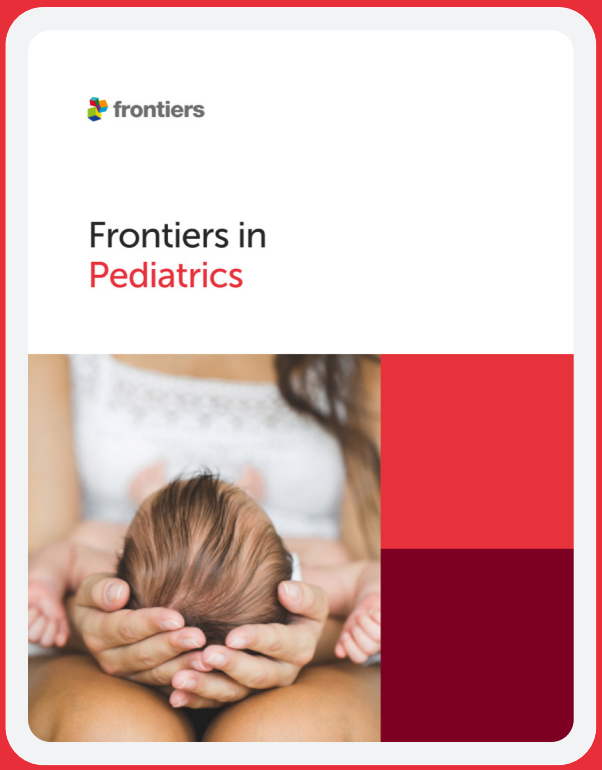

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