Maternal SARS-Cov-2 Infection and Associated Neonatal Sepsis: A Retrospective Multicenter Study in Jordan

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ABSTRACT

Background: Neonatal sepsis is a bloodstream infection that can lead to severe health complications in newborns, including permanent brain damage. The connection between maternal SARS-CoV-2 infection during pregnancy and neonatal sepsis is not yet completely understood.

Objective: To evaluate the frequency of neonatal sepsis in infants born to mothers who contracted SARS-CoV-2 during pregnancy.

Design: Retrospective multicenter observational case-control study.

Setting: Five hospitals in Jordan.

Method: A total of 184 participants were enrolled, with 93 COVID-19 positive mothers and 91 non-COVID-19 mothers serving as the control group. Maternal and neonatal data were obtained using a structured questionnaire in the National Electronic Health Database.

Results: The patient group had a higher frequency of COVID-19 infections prior to pregnancy than the control group (33.3% vs. 21%). Among COVID-19 positive mothers, 94.6% were infected once during pregnancy, with 52.7% experiencing moderate severity. Birth weight did not significantly differ between groups, except for extremely low birth weight (2.2% in patients vs. 1.1% in controls). Neonatal sepsis was detected in 5.4% of infants born to COVID-19 positive mothers but was absent in the control group. NICU admission was higher in the patient group (37.6%) than in the control group (31.9%). Significant associations were found between sepsis, COVID-19 severity, and NICU admission.

Conclusion: Maternal COVID-19 infection during pregnancy is linked to a higher risk of neonatal sepsis and NICU admission. These findings highlight the importance of careful monitoring and management of COVID-19 in pregnant women to mitigate potential adverse neonatal outcomes.

Keywords: Neonatal sepsis, maternal SARS-CoV-2 infection, pregnancy, NICU admission.

INTRODUCTION

SARS-CoV-2, the pathogen responsible for COVID-19, is a novel single-stranded RNA virus that has emerged as a result of various genetic alterations. It was initially identified in Wuhan, China, at the end of 2019. Since its emergence, SARS-CoV-2 has had a profound impact, leading to approximately 6,347,816 fatalities globally by July 2022, making it the most significant health crisis in recent times [2].

Pregnancy is typically accompanied by immunological changes that may increase the susceptibility to SARS-CoV-2 infection [3]. These infections can result in maternal and neonatal complications [4]. The outcomes of SARS-CoV-2 infections are influenced by various sociodemographic and pregnancy-related factors, such as maternal age, level of education, gestational age, and mode of delivery [5]. Infants delivered by mothers with SARS-CoV-2 may be susceptible to the virus and its detrimental effects.[6]. Systematic reviews have reported neonatal SARS-CoV-2 positivity rates ranging from 3.1% to 9.1% among newborns of infected mothers, with less than 1% reported in some studies. However, these studies were small and had limited results, raising concerns regarding publication bias [7, 8]. Furthermore,

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recent clinical case reports have documented late infections in the newborns of SARS-CoV-2 positive mothers. Despite numerous studies examining the potential for vertical transmission of SARS-CoV-2 from mother to fetus, the validity of this concept remains uncertain due to the lack of virus presence in amniotic fluid, umbilical cord blood, placenta, and breast milk specimens [9]. However, it has been proposed that SARS-CoV-2 transmission to neonates primarily occurs through respiratory droplets from infected caregivers [10].

Adverse maternal and neonatal outcomes of SARS-CoV-2 infection may include pregnancy-related hypertension and bleeding, need for ventilatory support, venous thromboembolism, increased maternal and neonatal critical care admissions, neonatal respiratory conditions following birth, preterm birth, stillbirth, low Apgar score, and high morbidity and mortality rates [11]. Most infected children showed mild symptoms and signs, but in some cases, the disease progressed to severe respiratory failure and sepsis [12]. Evidence linking SARS-CoV-2 infection to outcomes such as bleeding and hypertension during pregnancy is weak and conflicting. The potential consequences of infection according to the gestational age are yet to be fully understood. These uncertainties highlight the need for further research to confirm these associations and improve the care of pregnant women infected with SARS-CoV-2 [13].

Neonatal sepsis is a severe bloodstream infection caused by various pathogens, including viruses and bacteria. This infection poses significant health risks to newborns, including the potential for permanent brain damage, and is a leading cause of emergency neonatal hospital admissions. [14]. Transmission of the infection can occur either vertically during the labor process or horizontally as a result of direct contact between the baby and medical personnel, caregivers, or exposure to contaminated surroundings [15].

Neonatal sepsis was classified according to the World Health Organization (WHO) protocol based on its onset. Early onset sepsis (EOS) occurs within the first 72 h of life, whereas late-onset sepsis (LOS) occurs after 72 h. EOS is primarily caused by organisms acquired during the antenatal period, whereas LOS can be attributed to organisms acquired after labor (healthcare-associated infection) and is considered a recurrent complication of extended admission to the Neonatal Intensive Care Unit (NICU) after preterm birth [16].
Coagulase-negative Staphylococcus and Enterobacter cloacae are the most common causative pathogens of EOS, while coagulase-negative Staphylococcus and Staphylococcus aureus are the most common causative pathogens of LOS [17].

Evaluation of neonatal sepsis through blood tests can be a protracted process that may produce inaccurate negative outcomes. Thus, a comprehensive clinical evaluation incorporating the patient's medical history and existing test data is essential to quickly recognize the onset of sepsis and administer appropriate treatment while simultaneously pursuing additional diagnostic tests [18].

The present study sought to thoroughly evaluate the association between neonatal sepsis and maternal SARS-CoV-2 infection during pregnancy.

METHODOLOGY

Study Design: The current study implemented a retrospective, multicenter, observational case-control study across five Jordanian hospitals that were strategically selected to ensure diverse patient demographics, including Al Karak Governmental Hospital, Al Bashir Hospitals, Prince Ali Al Hussein Hospital, Al Hussein Center, and Jordan University Hospital. Cases were identified as newborns whose mothers tested positive for SARS-CoV-2 during pregnancy, whereas controls were recognized as newborns whose mothers did not test positive for SARS-CoV-2 during pregnancy.

Study Population: The research cohort comprised neonates born to mothers who had contracted SARS-CoV-2 infection during their pregnancy at the chosen hospitals between February and December 2022.

Inclusion Criteria

Neonates born to mothers with a PCR-confirmed SARS-CoV-2 infection during any trimester of pregnancy, along with the availability of comprehensive maternal and neonatal medical records, were eligible for inclusion in this study.

Exclusion Criteria

Mothers who exhibited clinical symptoms of COVID-19 during pregnancy, yet lacked confirmation through PCR testing, and newborns with incomplete medical records.

Data Collection : A structured questionnaire was used to obtain extensive data from the National Electronic Health Database (Hakeem). The questionnaire was developed using validated tools tailored to the requirements of this study. Information was collected on:

Maternal Information

Demographic Details: Age, contact information (address and telephone number). Obstetric History: Pregnancy status (gravidity and parity) and date of the last menstrual period. Chronic medical conditions included diabetes mellitus (DM), gestational DM, hypertension, gestational hypertension, preeclampsia, thyroid disease, obesity (BMI >35), and any other relevant medical conditions.

COVID-19 History

Number of infections during pregnancy, documentation of each infection through PCR, severity and course of each infection, history of COVID-19 before pregnancy, and vaccination details.

Our research analyzed the severity of COVID-19 infection using the NIH COVID-19 Treatment Guidelines. The following outline specifies the extensive requirements for categorizing infections into five classifications: asymptomatic, mild, moderate, severe, and critical disease. The classification structure is as follows: Asymptomatic/ Presymptomatic: Individuals who tested positive for SARS-CoV-2 and did not show any symptoms; Mild Illness: Individuals who have experienced symptoms of COVID-19, such as fever, cough, and loss of taste/smell, but have not experienced respiratory distress or abnormal chest imaging; Moderate Illness: Individuals who show signs of lower respiratory disease with an SpO2 level of ≥94% on room air; Severe Illness: Individuals with an SpO2 level <94% on room air, a PaO2/ FiO2 ratio <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%; Critical Illness: Individuals with respiratory failure, septic shock, or multiple organ dysfunction.

Neonatal Data

Apgar scores at 1 and 5 min, birth weight, length, and head circumference.
Clinical Consequences: Gestational age, NICU admission requirements, sepsis.

Data Management

To safeguard patient confidentiality, all the collected data were anonymized using unique identification codes. Electronic records were stored on password-protected computers with restricted access, whereas physical records were secured in locked cabinets.

Statistical Analysis

After collecting the necessary data, an initial examination was conducted to identify inconsistencies or missing values. The following statistical analyses were performed: descriptive statistics to profile the study population, inferential analysis involving chi-square tests to assess associations between categorical variables, T-tests or Mann-Whitney U tests to compare continuous variables based on their distribution. All analyses were conducted using SPSS software with a two-tailed significance level set at $P < 0.05$.

Ethical Considerations

Before commencing data collection, the researchers obtained ethical approval from the Mutah University Ethical Committee to ensure adherence to internationally recognized guidelines for medical research. The study design prioritized the protection of the rights, safety, dignity, and well-being of all participants, and informed consent was obtained from each participant's guardian. The process of obtaining consent highlighted the voluntary nature of the study and participants' right to withdraw from the study at any point in time without facing any adverse repercussions.

RESULTS

Table 1. Maternal, Neonates and Controls Demographic, History of COVID-19 Infection, Vaccination and Sepsis

Variables	Patients (mean ± SD) (no=93)	Controls (mean ± SD) (no=91)
Mother's age (years)	30.84±5.309	29.92±6.024
History of Covid-19		
- Prior to pregnancy	0.33±0.474	0.21±0.410
- Number of Covid-19 infections during pregnancy	1.06±0.288	0.00±0.000
Covid-19 infection		
- Severity (1=Mild, 2=Moderate, 3=Severe)	1.59±0.556	0.00±0.000
- Course (1=Hospital care, 2=Home care, 3=Outpatient)	1.96±0.292	0.00±0.000
Covid-19 vaccination		
- History	0.62±0.487	0.53±0.503
- Type	1.05±1.117	0.78±0.961
- Number of doses	1.27±1.044	1.01±1.013
Sepsis	0.05±0.227	0.00±0.000

Note: All values are presented as mean ± standard deviation (SD).

Table 1 presents the mean ± standard deviation (SD) of the variables collected for the study participant groups. The average age was 30.84 ± 5.309 years for the patient group and 29.92 ± 6.024 years for the control group. In terms of the history of COVID-19 infections, prior infections before pregnancy were observed in 0.33 ± 0.474 patients and 0.21 ± 0.410 controls. The number of COVID-19 infections during pregnancy was 1.06 ± 0.288 in the patient group, with no cases in the control group (0.00 ± 0.000). The severity of COVID-19 in the patient group was 1.59 ± 0.556, and the course of infection was 1.96 ± 0.292. In the control group, both the severity and course were 0.00 ± 0.000. The results for the history of vaccination, vaccine type, and number of vaccine shots were 0.62 ± 0.487 and 0.53 ± 0.503, 1.05 ± 1.117 and 0.78 ± 0.96, and for the number of vaccine doses, 1.27 ± 1.044 and 1.01 ± 1.013, for the patient and control groups, respectively. Sepsis was observed only in the patient group, with a mean value of 0.05 ± 0.227, and was not observed in the control group.

Table 2. The Frequency and Percentage of the Studied Variables

Variables	Frequency (n)	Percentage (%)
History of COVID prior to pregnancy		
Controls		
No	72	79
Yes	19	21
Patients		
No	62	66.7
Yes	31	33.3
Number of covid-19 infections during pregnancy		
1	88	94.6
2	4	4.3
3	1	1.1
Infection Course during pregnancy		
Hospital care	6	6.5
Home care	85	91.4
Outpatient	2	2.1
Infection severity *		
Patients		
Mild	41	44.1
Moderate	49	52.7
Severe	3	3.2
History of vaccination		
Controls		
No	40	47
Yes	51	53
Patients		
No	35	37.6
Yes	58	62.4
Number of doses of vaccine		
Controls		
0	40	44
1	6	6.6
2	39	42.8
3	6	6.6
Patients		
0	35	37.6
1	4	4.3
2	48	51.6
3	6	6.5
Birth weight		
Controls		
Normal	78	85.7
Large	2	2.2
Low birth weight	10	11
Extremely low birth weight	1	1.1
Patients		
Normal	79	84.9
Large	2	2.2
Low birth weight	10	10.8
Extremely low birth weight	2	2.2

Sepsis		
Controls		
No	91	100
Yes	0	0
Patients		
No	88	94.6
Yes	5	5.4
Neonatal ICU admission		
Controls		
No	62	68.1
Yes	29	31.9
Patients		
No	58	62.4
Yes	35	37.6

Note: Frequencies are presented as numbers (n) and percentages (%).

The data presented in Table 2 illustrates the frequencies and percentages of the analyzed variables in both the patient and control groups. The percentages of COVID-19 infection before pregnancy, history of vaccination, receiving two doses of the vaccine, sepsis, and neonatal ICU admission were higher in the patient group than in the control group (79%, 33.3%, 51.6%, 5.4%, and 37.6%, respectively) In the group of patients, the percentages of COVID-19 infection occurring once during pregnancy, receiving home care management, and experiencing moderate severity of infection were 4.3%, 91.4%, and 52.7%, respectively. Furthermore, the percentage of extremely low birth weight infants was higher in the patient group (2.2%) than in the control group (1.1%).

Table 3. Comparison of the frequencies of the studied variables in Covid-19 infected mothers and neonates versus controls using the chi-square test ($\chi 2$).

Variables	χ^2
Sepsis - patient versus control	0.008*
Sepsis and infection severity	0.025*
Sepsis and infection course	0.037*
Sepsis and history of Covid-19 prior to pregnancy	0.879
Sepsis and history of vaccination	0.125
Sepsis and type of vaccine	0.228
Sepsis and birth weight	0.213
Sepsis and Surfactant therapy	0.842
Infection severity and type of vaccine	0.298
Infection Severity and history of vaccination	0.229
NICU admission and type of vaccine	0.541
NICU admission - patient versus control	0.003*

* $p<0.05$

The results of the Chi-square analysis in Table 3 indicate a significant relationship between sepsis and the severity (P=0.025) and the course (P=0.037) of COVID-19 infection. A comparison between patients and controls revealed a significant difference in sepsis (P=0.008) and admission to the neonatal ICU (P=0.003). However, no significant association was observed between sepsis and history of COVID-19 prior to pregnancy (P =0.879), vaccination history (P =0.125), type of vaccine (P =0.228), birth weight (P =0.213), or surfactant therapy (P =0.842). Furthermore, no significant association was found between infection severity and vaccine type (P=0.298), vaccination history (P=0.229), or between vaccine type and neonatal ICU admission (P=0.541).

DISCUSSION

The effects of SARS-CoV-2 infection in adults have been extensively researched, and as community transmission continues to increase, it is crucial to investigate the impact of neonatal exposure to the virus [19]. Since the start of the COVID-19 pandemic, almost 58 million women between the ages of 15 and 40 have been infected with SARS-CoV-2 globally [20]. Surveys of universal screening revealed a prevalence of 6–8% among pregnant women [21]. Although vertical transmission of SARS-CoV-2 from mothers to newborns is uncommon [22], gestational infections can still pose risks to the fetus and newborn owing to activation of the maternal immune response [23, 24].
The current study involved 93 newborn infants born to mothers who tested positive for SARS-CoV-2 by RT-PCR at any point during their pregnancy. Conversely, 91 newborns born to non-infected mothers were included in the control group.

The results of this investigation indicated that the frequency of COVID-19 infection prior to pregnancy was higher among patients than among controls (33.3% vs. 21%). A single infection during pregnancy was the most prevalent (94.6%), whereas triple infections were rarely observed (1.1%). With respect to the severity of COVID-19 infection, moderate cases were the most prevalent (52.7%), while severe cases were the least frequent (3.2%). There was no significant difference in the frequency of normal, large, and low birth weights between the controls and patients, although the extremely low birth weight was slightly higher in the patient group (2.2% vs. 1.1% in controls). Neonatal sepsis was diagnosed in 5.4% of the patients but was not observed in the control group. The frequency of admission to the neonatal ICU post-COVID-19 was higher in patients (37.6%) than in the control group (31.9%). The results of the chi-square analysis indicated a significant relationship between sepsis and the progression and severity of COVID-19 infections. There was also a significant difference between the patients and controls regarding sepsis and neonatal ICU admission following infection.

According to a study by Chicea et al. [25], there was no significant impact of SARS-CoV-2 infection during birth on both maternal and neonatal outcomes, regardless of sociodemographic characteristics, timing of the pandemic, or SARS-CoV-2 variant. However, the researchers recommended additional research to explore the effects of infection during different stages of pregnancy, particularly in the early stages, on the fetus, newborn, and mother. Preterm birth was more prevalent among mothers infected with SARS-CoV-2. Furthermore, a smaller proportion of infants were admitted to neonatal units when their mothers contracted SARS-CoV-2 infection during the perinatal period. During the first six months of the pandemic in the UK, neonatal infection was not a common occurrence [26].

A study conducted at the Jimma Medical Center in Ethiopia analyzed the epidemiological trends of neonatal sepsis and their relationship with COVID-19 containment measures. The study found that neonatal sepsis was a common reason for admission to the neonatal ICU, with an overall incidence rate of 9.5%. The trends showed an unstable pattern, with periods of both decreasing and increasing. A significant decrease in the incidence of neonatal sepsis was observed during the initial COVID-19 lockdown from May 2019 to August 2020, followed by a sharp increase from August 2020 to December 2020. Another significant decrease was observed between December 2020 and August 2021. The study suggests a possible interrelationship between the fluctuating patterns of neonatal sepsis and stringent COVID-19 containment measures. However, the reduction in incidence is influenced by several factors, including healthcare services, environmental conditions, and maternal and neonatal factors [27].

During the COVID-19 pandemic, there was a marked increase in neonatal sepsis mortality rates in newborns with low birth weight and gestational age. Notably, there was no direct correlation between maternal COVID-19 infection and mortality rates in both mothers and newborns.

Several factors played a role in the elevated mortality rate, including the prematurity of the newborn's body systems, a compromised immune system, and the development of related health issues such as pneumonia, anemia, and necrotizing enterocolitis [28].
It is worth noting that there are certain similarities between severe COVID-19 cases and neonatal sepsis. Consequently, physicians must conduct a comprehensive patient history, closely monitor an individual's condition, and perform detailed laboratory tests to rule out other potential causes of sepsis beyond COVID-19. This thorough approach is essential for selecting the most appropriate and effective antibiotic treatment, which can help reduce the morbidity and mortality rates associated with sepsis [29]. However, there are some discrepancies between the results of our study and those reported in the medical literature. This could be due to the relatively small sample size, the lack of statistically significant results in various comparisons, and the fact that both study groups were from a single region in Jordan with different ethnic backgrounds compared to the participants in previous studies.

CONCLUSION

In this research endeavor, it was observed that the patient group exhibited a higher incidence of COVID-19 infection prior to pregnancy as compared to the control group. Moreover, single COVID-19 infections during pregnancy were most commonly observed among patients. The severity of COVID-19 infection was predominantly moderate among patients. It was also observed that the frequency of neonatal ICU admissions was higher in the patient group than in the control group. It was noted that there were no significant differences in birth weight between the two groups, with the exception of a higher incidence of extremely low birth weight in the patient group. Neonatal sepsis was diagnosed in 5.4% of patients and in none of the controls. A significant association was observed between neonatal sepsis and the course and severity of COVID-19 infection. Furthermore, significant differences were detected between the patients and controls with respect to sepsis and neonatal ICU admission post-infection. These findings emphasize the necessity of closely monitoring and managing pregnant women with COVID-19 to minimize adverse neonatal outcomes.

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Ethical Considerations: Before commencing data collection, the researchers obtained ethical approval from Mutah University (Approval Number: 1692024).

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Potential Conflicts of Interest: None

Competing Interest: None

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