Clinical Outcomes and Laboratory Values of Infants with COVID-19 among Several Maternal Variables: A Retrospective Cohort

Tal Bechor Ariel MD[1,2]*, Ben Ariel MD[1,2]*, Yuni Lahav MD[1,2], Moshe Yana BSc[1,2], Michael Ben-Acon MD[1,2], and Nechama Sharon MD[1,2]

[1]Department of Pediatrics, Sanz Medical Center–Laniado Hospital, Netanya, Israel
[2]Adelson School of Medicine, Ariel University, Ariel, Israel

ABSTRACT

Background: Infants younger than 6 months of age are not eligible for coronavirus disease 2019 (COVID-19) vaccinations. Maternal variables during pregnancy and the postnatal period may affect the clinical and laboratory course of COVID-19 positive infants.

Objectives: To assess the clinical manifestation and laboratory differences in infants with three maternal variables: breastfeeding, vaccinated, and co-illness.

Methods: We conducted a single-center retrospective cohort study of positive COVID-19 infants with three subgroups of maternal variables. The population included infants under 6 months of age hospitalized due to COVID-19. Data about clinical features, laboratory tests, and maternal information including vaccination status, breastfeeding status and maternal positive COVID-19 infection was gathered. All variables were compared among the three subgroups.

Results: Breastfed infants had shorter hospitalization period (mean 2.61 ± 1.378 days) compared to non-breastfed infants (mean 3.8 ± 1.549) (P = 0.051). COVID-19 infants of positive COVID-19 mothers had a higher absolute neutrophil count (mean 4.4 ± 3.8) compared to infants of COVID-19 negative mothers (mean 2.7 ± 2.4) (P = 0.042).

Conclusions: Breastfeeding was associated with shorter periods of hospitalization in COVID-19 positive infants. In addition, positive COVID-19 infants of mothers who were positive for COVID-19 are likely to have a higher absolute neutrophils count.

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KEY WORDS: breastfeeding, coronavirus disease 2019 (COVID-19), hospitalization, infant, vaccination

*These authors contributed equally to this study

In December 2019, COVID-19 was first introduced in Wuhan, China. On 20 January 2020, the first pediatric case of the novel coronavirus infection was confirmed in Shenzhen, China [1]. The first case of an infant diagnosed with COVID-19 was reported in a 3-month-old female infant with fever on 26 January 2020 [2].

Since then, millions of children have been diagnosed with COVID-19. The common clinical manifestations of symptomatic patients include presentation of fever, dry cough, fatigue, and sometimes gastrointestinal symptoms. The pediatric population usually shows mild symptoms with a good prognosis and a recovery time of 1–2 weeks. Laboratory findings in children showed a normal or elevated white blood cell count and normal or low lymphocyte count in most cases, which suggests less immune dysfunction after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the pediatric population [3].

COVID-19 mRNA vaccinations were developed and are now available for children over 6 months of age and pregnant women in all trimesters. COVID-19 in pregnancy is associated with neonatal risks, adverse pregnancy outcomes, and both maternal and neonatal complications [4].

Maternal vaccination may have dual benefits. Vaccination provides pregnant women with protection and may also provide the added benefit of protecting their infants, who would not be eligible for vaccination [5-7]. COVID-19 vaccination during pregnancy leads to the presence of detectable maternal antibodies in cord blood, breast milk, and serum specimens obtained from infants, findings that indicate the transfer of maternal antibodies to infants. Moreover, the anti-spike antibodies against COVID-19 may persist through the first 6 months of life, and these antibody levels are higher among infants born to mothers who were vaccinated during pregnancy than among infants whose mothers had antibodies induced by natural SARS-CoV-2 infection during pregnancy [8].

During the peak period of the Omicron (B.1.1.259) variant of COVID-19, hospitalization rates among infants younger than 6 months of age who were infected were six times as high as the rates during the Delta (B.1.617.2) variant peak. A reduced risk of hospitalization was previously shown (regarding the Delta wave) in infants whose mothers were vaccinated during pregnancy [9].

We tested a population of 34 COVID-19 positive infants aged 0–6 months who had been admitted to the pediatric department at Laniado Hospital. We investigated three maternal variables: vaccinated mothers, breastfeeding mothers, and COVID-19 positive mothers to assess the clinical and laboratory changes among the groups.

PATIENTS AND METHODS

STUDY DESIGN

We conducted a single-center cohort study, which included 34 hospitalized infants younger than 6 months of age who had tested positive for COVID-19. Patients were divided into three subgroups according to different maternal variables: breastfeeding status, vaccination status, and positive for COVID-19 at the time of her infant's illness. These subgroups were retrospective cohorts to assess the different laboratory and clinical hospitalization information of COVID-19 positive infants.

STUDY POPULATION

Study participants were younger than 6 months of age and were identified between 1 November 2021 and 20 August 2022 in the pediatric department at our hospital. The participants were identified through a review of hospital medical records of infants who tested positive for COVID-19 or presented with clinical symptoms as the main reason for admission. All the infants had a positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) test within 48 hours of hospital admission.

The different mother variables were evaluated through the mother's self-report of vaccination status, COVID-19 co-morbidity, and breastfeeding status [Table 1]. Informed consent was obtained from both parents of the participants. The study was approved by the Laniado hospital review board.

INCLUSION CRITERIA

Infants younger than 6 months of age, who were admitted with a positive COVID-19 PCR or antigen test were included.

EXCLUSION CRITERIA

Exclusion criteria included infants taking steroids or with a background of hematologic disease.

STATISTICAL ANALYSIS

We performed a two-way Mann-Whitney U test to compare the levels of different laboratory parameters (white blood cell count, hemoglobin levels, platelet count, neutrophils, lymphocytes, C-reactive protein) and clinical information (days of hospitalization, fever, and oxygen saturation levels [SAT%]) between the breastfeeding and non-breastfeeding group, the vaccinated and non-vaccinated mothers' group, and the positive and negative COVID-19 results of the mothers.

RESULTS

Our analysis included a total of 34 infants younger than 6 months of age who were admitted to the pediatric department

Table 1. Patient characteristics in the three subgroups

	Breastfed infants (n=18)	Non-breastfed infants (n=10)
Mean age in months	1.58 ± 1.16	3.06 ± 2.13
Sex		
Male (%)	9 (50)	8 (80)
Female (%)	9 (50)	2 (20)
Underlying health conditions/total number (%)	4/18 (22.2)	2/10 (20)
	Positive COVID-19 mothers (n=19)	**Negative COVID 19 mothers (n=15)**
Mean age in months	2.19 ± 1.93	1.87 ± 1.17
Sex		
Male (%)	8 (42)	11 (73)
Female (%)	11 (58)	4 (27)
Underlying health conditions/total number (%)	5/19 (26.3)	3/15 (20)
	Vaccinated COVID-19 mothers(n=16)	**Non-vaccinated COVID 19 mothers (n=17)**
Mean age in months	2.05 ± 1.47	2.08 ± 1.85
Sex		
Male (%)	8 (50)	11 (65)
Female (%)	8 (50)	6 (35)
Underlying health conditions/total number (%)	5/16 (31.2)	3/17 (17.6)

Percentages may not total 100 because of rounding. The data were based on parent self-reports. Data were missing for six infants in the breastfed group and for one infant in the vaccinated mothers group. Underlying health conditions included cardiovascular diseases, infectious diseases, immunosuppression, autoimmune disorders, and genetic disorders.

in Laniado Hospital due to COVID-19 illness. We compared the following laboratory and clinical parameters among the three subgroups: total white blood cell count, hemoglobin levels, platelet count, neutrophils differential (Neutro, Neutro%), lymphocytes differential (Lympho, Lympho%), C-reactive protein levels, SAT%, presence of fever, and days of hospitalization [Table 2].

BREASTFED INFANTS VS. NON-BREASTFED

We found fewer days of hospitalization in the breastfed infant group (mean 2.61 ± 1.378) compared to non-breastfed infant groups (mean 3.8 ± 1.549), although it almost met statistical significance ($P = 0.051$). In all other parameters we did not find any significant differences [Table 2].

**INFANTS OF COVID-19 POSITIVE MOTHERS COMPARED
TO COVID-19 NEGATIVE MOTHERS
AT THE TIME OF THE INFANT'S DISEASE**

When comparing positive COVID-19 mothers to negative mothers, we found a difference in the absolute neutrophils count. Infants of mothers who were COVID-19 positive at the same time as their infant showed higher absolute neutrophils count (mean 4.4 ± 3.8) compared to infants of mothers who were COVID-19 negative at the time of infant's disease (mean 2.7 ± 2.4) with statistical significance ($P = 0.042$). In all other parameters we did not find any statistically significant difference [Table 3].

**INFANTS OF COVID-19 VACCINATED MOTHERS VS.
NON-VACCINATED MOTHERS**

We did not find any statistically significant differences among the infants of COVID-19 vaccinated mothers compared with non-vaccinated mothers between the different parameters [Table 4].

Table 2. Breastfed vs. non-breastfed infants

	Breastfed infants (n=18)	Non-breastfed infants (n=10)	*P*-value
Days of hospitalization	2.61 ± 1.378	3.8 ± 1.549	**0.051**
Fever, number/total (%)	13/18 (72.2)	9/10 (90)	0.464
Oxygen saturation levels	98.36 ± 1.781	97.5 ± 0.316	0.441
White blood cell count	10.467 ± 4.7593	13.25 ± 2.268	0.265
Hemoglobin levels	12.633 ± 2.041	12.34 ± 6.4504	0.621
Platelets count	392.83 ± 113.1	441.9 ± 147.29	0.464
Neutro%	32.267 ± 15.3682	36.78 ± 15.8144	0.356
Neutro	3.3 ± 2.2539	5.5 ± 4.9958	0.16
Lympho%	45.383 ± 16.6593	43.76 ± 15.1777	0.654
Lympho	5 ± 3.1264	5.16 ± 1.4073	0.654
C-reactive protein	2.1494 ± 2.18764	47.0978 ± 127.79771	0.229

P-value was calculated by using the Mann-Whitney U test. The fever parameter was binary
and is presented as number of infants with fever out of the total group.
Bold indicates significance.
Lympho = lymphocytes, Lympho% = lymphocytes differential, Neutro = neutrophils, Neutro% = neutrophil differential

Table 3. Positive COVID-19 mothers vs. negative COVID-19 mothers

	Positive COVID-19 mother (n=19)	Negative COVID-19 mothers (n=15)	*P*-value
Days of hospitalization	3.16 ± 1.5	3.07 ± 1.71	0.758
Fever, number/total (%)	14/19 (74)	13/15 (86)	0.537
Oxygen saturation levels	98.07 ± 1.9	97.46 ± 2.9	0.756
White blood cell count	11.68 ± 5.64	9.47 ± 4.88	0.271
Hemoglobin levels	12.93 ± 2.5	12.19 ± 1.84	0.947
Platelets count	411 ± 144	399 ± 83	0.986
Neutro%	36.67 ± 16	28.91 ± 14	0.199
Neutro	3.82 ± 3.38	2.79 ± 2.49	**0.042**
Lympho%	42.48 ± 14.95	47.45 ± 17.03	0.271
Lympho	4.95 ± 2.79	4.5 ± 2.3	0.733
C-reactive protein	24.61 ± 95.53	3.05 ± 5.34	0.483

P-value was calculated by using the Mann-Whitney U test. The fever parameter was binary
and is presented as number of infants with fever out of the total group.

Bold indicates significance.
Lympho = lymphocytes, Lympho% = lymphocytes differential, Neutro = neutrophils, Neutro% = neutrophil differential

Table 4. Vaccinated mothers vs. non-vaccinated mothers

	Vaccinated mothers (n=16)	Non-vaccinated mother (n=17)	*P*-value
Days of hospitalization	2.81 ± 1.64	3.4 ± 1.505	0.217
Fever, number/total (%)	13/16 (81)	13/17 (76)	0.817
Oxygen saturation levels	97 ± 2.74	98.5 ± 1.679	0.145
White blood cell count	9.1 ± 3.02	12.631 ± 6.68	0.138
Hemoglobin levels	12.4 ± 1.82	12.9 ± 2.69	0.838
Platelets count	420.5 ± 144.82	400.4 ± 93.9	0.838
Neutro%	30.8 ± 13.33	35.04 ± 17.88	0.642
Neutro	2.68 ± 1.35	4.8 ± 4.49	0.27
Lympho%	47.3 ± 11.85	43.2 ± 18.77	0.423
Lympho	4.4 ± 1.98	5.2 ± 3.01	0.254

P-value was calculated by using the Mann-Whitney U test. The fever parameter was binary
and is presented as number of infants with fever out of the total group.

Lympho = lymphocytes, Lympho% = lymphocytes differential,
Neutro = neutrophils, Neutro% = neutrophil differential

DISCUSSION

We found that maternal breastfeeding during the first months of life (infants younger than 6 months of age) was associated with fewer days of hospitalization in COVID-19 positive infants during the circulation of the Omicron variant. We did not find any difference in the laboratory evaluation among infants who were breastfed compared with non-breastfed infants. All infants had normal neutrophil and lymphocyte counts. Lymphopenia is associated with severe disease among hospitalized patients. In addition, lymphopenia is seen in about one-third of children with COVID-19 [3,10].

We presented 34 cases of hospitalized infants, most of whom had a normal lymphocyte count. This finding may suggest a different laboratory characteristic for positive COVID-19 infants compared with the pediatric population over 6 months of age and with the adult population.

The finding that breastfeeding shortens the length of hospitalization in positive COVID-19 infants provides evidence of additional benefit of maternal breastfeeding, as was previously shown in many previous studies and as recommended by the World Health Organization and U.S. Centers for Disease Control and Prevention [11-16].

In this study we used a small sample size of positive COVID-19 infants. Perhaps a bigger sample size would have demonstrated further advantages of maternal breastfeeding other than shortening hospitalization days. Moreover, further questions arise from this finding, mostly regarding the prevention of hospitalization among COVID-19 infants who are breastfed. A larger cohort including non-hospitalized positive COVID-19 infant patients should be collected and evaluated.

We found a higher number of absolute neutrophils count among positive COVID-19 infants whose mothers were positive for COVID-19 at the same time. Although this finding is of clinical importance, the mean difference was less than 1000 cells, meaning there was almost no laboratory difference between the two groups. Neutrophils counts for both groups were considered within the normal range [15].

When examining the infants of vaccinated mothers compared with non-vaccinated, we did not find any laboratory or epidemiologic differences. In previous studies we found that COVID-19 vaccinations had a variety of benefits regarding morbidity and mortality, prevention of hospitalization, better clinical presentation, fewer complications, and critical illness [4,9,16-20]. In our study we did not examine all these parameters, but we would have expected some differences in the laboratory parameters. We believe a larger cohort would have demonstrated these differences.

Correspondence

Dr. N. Sharon
Dept. of Pediatrics, Sanz Medical Center–Laniado Hospital, Netanya 42150, Israel
Phone: (972-9) 860-4739
Email: nsharon@laniado.org.il

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Sin is geographical.

Bertrand Russell (1872–1970), British philosopher, mathematician, author, and Nobel laureate

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Capsule

Intermittent fasting plus early time-restricted eating versus calorie restriction and standard care in adults at risk of type 2 diabetes: a randomized controlled trial

Intermittent fasting appears to be an equivalent alternative to calorie restriction (CR) to improve health in humans. However, few trials have considered applying meal timing during the fasting day, which may be a limitation. **Teong** et al. developed a novel intermittent fasting plus early time-restricted eating (iTRE) approach. Adults (n=209, 58 ± 10 years of age, 34.8 ± 4.7 kg m−2) at increased risk of developing type 2 diabetes were randomized to one of three groups (2:2:1): iTRE (30% energy requirements between 0800 and 1200 hours and followed by a 20-hour fasting period on three nonconsecutive days per week, and ad libitum eating on other days); CR (70% of energy requirements daily, without time prescription); or standard care (weight loss booklet). This open-label, parallel group, three-arm randomized controlled trial provided nutritional support to participants in the iTRE and CR arms for 6 months, with an additional 12-month follow-up. The primary outcome was change in glucose area under the curve in response to a mixed-meal tolerance test at month 6 in iTRE versus CR. Glucose tolerance was improved to a greater extent in iTRE compared with CR (-10.10 (95% confidence interval -14.08 to -6.11) versus -3.57 (95% confidence interval -7.72 to 0.57) mg dl−1 min−1; P = 0.03) at month 6, but these differences were lost at month 18. Adverse events were transient and generally mild. Reports of fatigue were higher in iTRE versus CR and standard care, whereas reports of constipation and headache were higher in iTRE and CR versus standard care. Incorporating advice for meal timing with prolonged fasting led to greater improvements in postprandial glucose metabolism in adults at increased risk of developing type 2 diabetes.

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Eitan Israeli