

Newborns born to mothers with a history of COVID-19 during pregnancy, delivery and/or postpartum: 52 cases of neonatal intensive care experience

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ABSTRACT

Objective: The effect of the Covid-19 pandemic on the prenatal and neonatal periods is not yet fully understood. Therefore, this study aimed to prospectively evaluate and investigate the clinical features of newborns who were born to mothers with a history of Covid-19 during pregnancy, delivery, and/or postpartum.

Patient and Methods: The study prospectively evaluated 52 newborns born to mothers with a history of Covid-19 during pregnancy, delivery, and/or postpartum followed in our hospital's neonatal intensive care unit between November 2020 and May 2022.

Results: Unvaccinated mothers of 12 babies with Covid-19 IgG antibody positivity + severe pneumonia in their clinical course and/or chest X-ray stated that they did not have a history of Covid-19. It was found that attachment to intermittent mechanical ventilation (SIMV) in infants with a Covid-19 -infected father was statistically significantly higher than in infants with a non-infected father. The rate of being connected to synchronized intermittent mechanical ventilation (SIMV) in babies whose both parents had Covid-19 was statistically significantly higher than in the babies whose fathers did not have Covid-19 (p:0.030; p<0.05).

Conclusion: Newborns born to mothers suspected or confirmed to be Covid-19-positive are mostly asymptomatic, suspected cases or cases with a severe or unusual clinical course should be investigated for Covid-19 even if there is no maternal history. In newborns, not only the mother but also the father should be questioned for Covid-19, as both parents being infected will increase the viral load.

Keywords: Newborn, Pregnancy, COVID-19 vaccine, NICU, Pandemic, SARS-CoV-2

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INTRODUCTION

COVID-19 is a disease caused by a virus from the family Coronaviridae of viruses first described in China in December 2019 and spread rapidly throughout the world in a short time (1). Almost all the 145 million annual births worldwide are at risk, including the nearly 400,000 babies born each day (2). As the number of patients who get pregnant and give birth during this period increases, knowledge on clinical data on the mother and baby, and the effects on newborns is constantly updated. However, the effect of the Covid-19 pandemic, which has affected the whole world, on the prenatal and neonatal periods, remains unclear (3).

In this study, the authors first aimed to prospectively evaluate and investigate the clinical features of newborns born to mothers with a history of Covid-19 during pregnancy, delivery, and/or postpartum, and newborns with an unusual clinical course even without a maternal history. The second aim was to investigate the effect of the Covid-19 status of the mother and father on the baby, while the third aim was to investigate the effect of the mother's comorbidities on the infant's clinical conditions.

MATERIALS AND METHODS

This prospective study was performed in NICU from November 2020 to May 2022. Birth weight, gestational week, delivery type, gender, five-minute Apgar scores, ventilator support, length of stay, hemogram biochemistry and C-Reactive Protein (CRP) results of the patients included in the study were recorded together with maternal and birth characteristics, and the father's Covid-19 history. The 25(OH) vitamin D levels of the babies with hypocalcemia and their mothers were measured. Infants with a positive history of SARS-CoV-2 at birth or during pregnancy and/or an unusual clinical course were tested for Covid-19 with rRT-PCR analysis from a nasopharyngeal swab and an antibody test from blood.

Maternal socio demographic factors such as age, number of pregnancies, smoking status, comorbidities, history of SARS-CoV-2 and vaccination status were examined. In those with a maternal history of SARS-CoV-2, paternal history was also questioned and recorded. The SARS-CoV-2 test was performed on the nasopharyngeal swab obtained from each mother at birth. AFIAS COVID-19 Ag (Foresan immunological) (Boditech Med., Chuncheon-si, Gang-won-do, Republic of Korea) test was used to detect IgM and IgG specific to SARS-CoV-2. The results were interpreted according to the cut-off index (COI) determined using an equation based on the sample-positive-control signal ratio. $COI < 1.0$ was considered "negative" and $COI \geq 1.0$ was considered "positive" for the SARS-CoV-2 antigen. Whether the father also had Covid-19 together with the mother was questioned during hospitalization.

This study was approved by the ethics commission of special Afiyet Hospital(17.02.2022/98). Informed consent was obtained from the guardians of all the included patients. Transient tachypnea of the newborn (TTN) was defined as respiratory distress occurring in term or near-term babies, emerging within 4-6 h of delivery, which generally resolved within three days. Respiratory Distress Syndrome (RDS) was defined as tachypnea, chest wall retractions and cyanosis with room air, showing persistence or progression for the initial 48-96 h, together with characteristic reticulogranular appearance and air bronchograms in the chest X-ray(3). The diagnosis of congenital pneumonia was made based on risk factors, physical examination, clinical findings, radiological findings, and laboratory tests (4,5).

Statistical analysis

While evaluating the results obtained from the study, IBM SPSS Statistics 22 (SPSS IBM) software was used for the statistical analysis. For the evaluation of the study data, the Shapiro-Wilk normality test was used to assess whether the parameters follow a normal distribution. In the evaluation of the study data, the Mann Whitney U test was used to compare the descriptive statistical methods (mean, standard deviation and frequency), as well as quantitative data and non-normally distributed parameters between the two groups. The Chi-square test was used to compare the qualitative data. The Spearman's rho correlation analysis was used to examine the correlations between the non-normally distributed parameters. A value of $p < 0.05$ was considered as the level of significance.

RESULTS

The study prospectively evaluated 52 newborns born to mothers with a history of Covid-19 during pregnancy, delivery and/or postpartum, followed in our hospital's neonatal intensive care unit between November 2020 and May 2022. The study population newborns was tested for Covid-19. SARS-CoV-2 reverse transcriptase-polymerase chain reaction of the throat swab from the neonates was negative.

The study population was newborns; 37 (71.1%) were male, 15 (28.8%) were female, 37 (71.1%) were term, and 15 (28.8%) were preterm infants. One of the premature babies was from a twin pregnancy. Birth weight was 3098.59 ± 648.27 (1550 – 4165 g), mean hospitalization time was 13.96 ± 9.92 days, and the 5-min Apgar score was 8.57 (1,34). The most frequent hospitalization diagnoses were transient tachypnea of the newborn (TTN) in 14 (26.9%) newborns, sepsis in 14 (26.9%), congenital pneumonia in 12 (23.0%), respiratory distress (RDS) in 5 (9.6%), asphyxia in 2 (3.8%), TTN + sepsis in 2 (3.8%), bronchopneumonia + bronchiolitis in 2 (3.8%), and sepsis + urinary tract infection (UTI) in 1 (1.9%). Clinical characteristics and laboratory results of the newborns are shown in **Table 1**.

Unvaccinated mothers of 12 babies with Covid-19 IgG antibody positivity + severe pneumonia in their clinical course and/or chest X-ray stated that they did not have a history of Covid-19. Out of all the mothers, eight stated that they had the flu, and 2 had URTI. Two mothers had no history of infection. The parents and siblings of one of the two infants with severe bronchopneumonia were also positive for SARS-CoV-2 IgG antibodies. The respiratory syncytial virus antigen test was positive in the nasal swab of the other bronchopneumonia case.

25 (OH) vitamin D deficiencies were detected in 11 (21.1%) babies and their mothers. The 25(OH) vitamin D levels were 12.7 ± 1.15 and 12.4 ± 1.12 ng/ml in infants and mothers, respectively. Echocardiography was performed on four infants in total. Persistent pulmonary hypertension was detected in the term infant who had congenital pneumonia and was given surfactant twice. It improved with conservative treatment. Physical examination revealed atrial septal defect (ASD) due to murmur in 2 of the three premature babies and ASD+patent ductus arteriosus (PDA) in the 31-week-old premature baby. PDA was treated with paracetamol for four days.

All infants were fed with breast milk, except for 3. One of the mothers was Covid positive at birth + received treatment in the intensive care unit, and thus, she could not give breast milk to her newborn. The other baby's parents could not bring breast milk because they were isolated at home due to Covid. The twin babies could not be fed with breast milk because their mothers did not want it.

The study consisted of a total of 51 mothers due to twin pregnancy of one of the mothers. The mean age of the mothers was 29.67 ± 5.87 years, and the mean number of pregnancies was 2.28 (range: 1-38). The parents of 8 of the newborns were together, and 2 of the mothers were infected with Covid-19 twice during pregnancy. SARS-CoV-2 reverse

transcriptase-polymerase chain reaction of 14 mothers' throat swab just before birth was positive.

Two of the mothers had been treated for Covid-19. One of these mothers was followed up by intensive care hospitalization + steroid treatment and the other by outpatient treatment. Forty-five (88.2%) mothers were unvaccinated. After October 2021, when the vaccination of the pregnant women started in our country, 6 (33.3%) out of every 20 pregnant women were vaccinated against Covid-19. Data on mothers and fathers are shown in **Table 2**.

A total of 35 (68.6%) mothers had comorbidities. Four mothers had a smoking history. The most common comorbidities were urinary tract infection and gestational diabetes (**Table 3**). The Covid-19 infection rate of mothers with comorbidities (68.6%) was statistically significantly higher than that of mothers without comorbidities (31.3%) ($p=0.039$, $p<0.05$).

There was no statistically significant difference in terms of hospital stay, SIMV, CPAP and Hood and O2 in infants of mothers who had Covid-19 at birth and mothers who had Covid-19 in other months ($p>0.05$).

There was no statistically significant difference in terms of hospital stay, CPAP, Hood and O2 between infants whose fathers also had Covid-19 and those whose fathers did not have Covid-19 ($p>0.05$). However, attachment to SIMV in infants with a Covid-19 infected father was statistically significantly higher than in infants with a non-infected father ($p:0.030$; $p<0.05$). The seasonal distribution of the patients was as follows: 19 (36.5%) patients in the winter, 18 (34.6%) in the spring, 12 (23%) in the autumn and 3 (5.7%) patients in the summer. The prevalence of Covid-19 showed a statistically significant difference between the seasons ($p:0.011$; $p<0.05$). In the current study, the maternal and infant mortality rate was zero.

Table 1: Clinical characteristics and laboratory results of the neonates

		Min-Max	Mean±SS (median)
Birth weight		1550-4165	3098,59 (648,27 (3242,5)
Gestational age		31-40	37,26 (2,28 (38))
Apgar score .5.minute		4-10	8,57 (1,34 (9)
Hospitalization time (days)		5-45	13,96 (9,92 (11))
		N=52	%
Gender	Female	15	28,8
	Male	37	71,1
Delivery mode	Cesarean	42	80,7
	Vaginal delivery	10	19,2
Surfactant	Yes	11	21,1
	No	41	78,8
Disease	TTN	14	26,9
	Sepsis	14	26,9
	Congenital pneumonia	12	23,0
	RDS	5	9,6
	Asphyxia	2	3,8
	TTN+Sepsis	2	3,8
	Bronchopneumonia + Bronchiolitis	2	3,8
	Sepsis+ UTİ	1	1,9
Covid-19 IgG (COI)		5-103	24,17(8,1)
SIMV		0-10	1,52(2,47)
CPAP		0-10	2 (2,64)
HOOD		0-18	3,7 (3,96)
25(OH) vitamin D(n=11)			12,7 (1,15 ng/ml)

TTN: Transient tachypnea of the newborn; RDS: Respiratory distress syndrome; UTI: Urinary tract infection; SIMV: Synchronized intermittent mechanical ventilation; CPAP: Continuous positive airway pressure

Table 2: Demographic data of the parents

N=51		Min-Max	Ort±SS (median)
Mother's age		20-43	29,67 (5,87 (29))
Number of pregnancies		1-6	2,28 (1,38 (2))
2 Time Covid-19		n:2	%3,9
		No=51	%
Mother treatment	Yes	2	3,9
	No	49	96,0
Maternal comorbidity	Yes	35	68,6
	No	16	31,3
Maternal Covid-19 time	Unknown	12	23,5
	At birth	14	27,4
	Other months	25	49,0
Smoker	Yes	4	7,8
	No	47	92,1
Mother vaccine	1 dose	6	11,7
	2 dose	2	3,9
	None	45	88,2
Fathers Covid-19 positivity	Yes	8	15,6
	No	43	84,3

Table 3: Maternal Comorbidities

Mother Comorbidities	N=51	%
Asthma	1	1,9
Tooth infection	1	1,9
GDM	5	9,8
GDM+Hypertension+UTI	5	9,8
HCV+Thyroid Disease	1	1,9
Hypertension	1	1,9
UTI	9	17,6
UTI+Influenza	2	3,9
UTI+Thyroid Disease	1	1,9
Genital Fungal Infection	3	5,8
Preeclampsia	1	1,9
Thyroid Disease	2	3,9
URTI	2	3,9
Varicose	1	1,9
None	16	31,3

UTI: Urinary tract infection; GDM: Gestational diabetes mellitus; URTI: Upper Respiratory Tract Infection; HCV: Hepatit C virus

DISCUSSION

The 2019 coronavirus pandemic (Covid-19), which emerged in the past years, has seriously affected public health worldwide, and its effect still continues. The suppression of the immune system during pregnancy can make the mother vulnerable to infectious diseases and increase her risk of becoming infected with numerous viruses and bacteria, including coronavirus. Accordingly, it is reported in the literature that pregnant women and newborns are at greater potential risk during the Covid-19 pandemic (5-10). Due to increased morbidity and mortality, it is recommended to follow pregnant women and newborns more closely (11).

There is little evidence of a possible effect of Covid-19 in early pregnancy (<12 weeks). In the late pregnancy period (>24 weeks) (12,13), based on the impact of other viral infections, it can be predicted that COVID-19 infection may cause increased rates of adverse pregnancy outcomes such as fetal growth restriction, preterm delivery and perinatal mortality.

Some infants born to mothers with Covid-19 have increased concentrations of both immunoglobulin (Ig)M and IgG for SARS-CoV-2 (14,15). Although, IgG can be passively transferred from the mother to the baby in the uterus, IgM has a larger molecular weight and cannot cross the placenta. Most studies on newborn outcomes reported no serious adverse consequences in newborns born to SARS-CoV-2 positive mothers (16-19). One study determined the frequency of asymptomatic SARS-CoV-2 positive women as 6.3% in whites, 20% in Asians, and 3.4% in women from mixed and other ethnic origins (20). In the present study, unvaccinated mothers of 12 babies with Covid IgG antibody positivity + severe pneumonia in their clinical course and/or chest X-ray stated that they did not have a history of Covid. It was found that attachment to SIMV in infants with a Covid-infected father was statistically significantly higher than in infants with a non-infected father.

There are many publications in the literature on the outcomes for newborns of Covid-infected mothers. However, to the best of the author's knowledge, there is no data on fathers. Since both parents having Covid-19 would increase the viral load, these babies were followed in SIMV. Therefore, it is believed that the current study will significantly contribute to the literature.

In general, the incidence of congenital pneumonia is <1% in term infants and approximately 10% in premature infants (21-23). Considering all cases followed in our neonatal intensive care unit of about ten years old, congenital pneumonia cases have never been this common until the pandemic. There was extensive infiltration on chest radiographs. One of the infants recovered with two treatments of surfactant + broad-spectrum antibiotic.

In a study conducted using 79 mothers, 15 (18.98%) were found to be positive for SARS-CoV-2, and 60% of the tested mothers were asymptomatic. This study found no association between smoking, alcohol use, positive urine drug screening, comorbidities or antenatal infection, and maternal SARS-CoV-2 status (24). In the present study, the rate of Covid-infection of mothers with comorbidity (68.6%) was found to be statistically significantly higher than those without comorbidity (31.3%).

In a study previously conducted in our neonatal intensive care unit, vitamin D deficiency/insufficiency was found in 99.4% of the infants and vitamin D deficiency/insufficiency in 96.8% of the mothers (25). After this study, vitamin D was given routinely in the obstetrics clinic. In the present study, the detection of 25 (OH) vitamin D deficiencies in 11 (21.1%) babies and their mothers was regarded as a positive development.

It was found that 88% of all the pregnant women who applied to give birth in London and New York, whose routine nose/throat swab test results were positive, were asymptomatic (20,26). In the present study, the nasal/throat swab test routinely performed on every pregnant woman who came for delivery detected positivity in 14 (27.4%) pregnant women. Two pregnant women had symptoms, and 12 (85.7%) were asymptomatic. One of the mothers was followed up in the intensive care unit, while the other was treated as an outpatient.

It is unclear whether SARS-CoV-2 is transmitted through breast milk. Current guidelines recommend that mothers continue to breastfeed even if their tests are positive during delivery and in the postpartum period. According to these guidelines, women with confirmed Covid-19 should wear a medical mask when feeding, and follow basic hygiene recommendations, including hand washing (27). In our unit, breast milk was given after explaining the N95 mask + hand washing + general hygiene rules. All infants were fed with breast milk, except for 3. One of the mothers was Covid positive at birth + received treatment in the intensive care unit, and thus, she could not give breast milk to her newborn. The other baby's parents could not bring breast milk because they were isolated at home due to Covid. The twin babies could not be fed with breast milk because their mother did not want it. There were no complications related to breastfeeding. Immunization of pregnant women against COVID-19 is

crucial to minimize the risks of Covid-19 during pregnancy, so vaccination is recommended regardless of gestational age.

Although, the Covid-19 vaccine application started in our country in January 2021, it started to be administered to pregnant women after the Turkish Ministry of Health updated the treatment guidelines in October 2021. The recommendation of the Ministry about vaccinations in pregnant women is that pregnant women should be vaccinated after the first trimester, if possible, by being informed and of their own will. After October 2021, when the vaccination of pregnant women began in our country, 6 out of every 20 pregnant women (33.3%) were vaccinated against COVID-19. Although pregnant women have shown some enthusiasm for getting the vaccine recently, many remain undecided due to the newness of the vaccine. While all available evidence supports the safety of administering currently available SARS-CoV-2 vaccines before, during, and after pregnancy, expectant mothers are concerned as it is a new vaccine. As the scientific data during pregnancy increases, and as health authorities and obstetricians inform the expectant mothers about vaccination, it is hoped that the vaccination rates further increase.

CONCLUSION

In conclusion, SARS-CoV-2 continues to be a significant cause of mortality and morbidity worldwide. While newborns born to mothers suspected or confirmed to be Covid-positive are mostly asymptomatic, suspected cases or cases with a severe or unusual clinical course should be investigated for Covid-19 even if there is no maternal history. In newborns, not only the mother but also the father should be questioned for Covid-19, as both parents being infected will increase the viral load.

Limitations: All mothers could not be tested because of the cost of SARS-CoV-2 Ig G. Maternal symptoms could not be recorded because some mothers could not remember the date of their Covid-19 infection. Since the vaccination of pregnant women started after October 2021 in our country, the rate of vaccination of mothers has been low. Although pregnant women have shown some enthusiasm for getting the vaccine recently, many remain undecided due to the newness of the vaccine. When we asked mothers why they did not get vaccinated, we observed that they abstained due to misinformation they heard from their environment and/or social media, and because their obstetricians did not provide them with enough information about vaccination.

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Author Contributions: NCK, AF; designed the study, collected the data and performed the data analysis. All authors revised the data analysis, edited the manuscript and critically revised the final version. AF; submitted the manuscript. All authors read and approved the manuscript

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Written consent was obtained from each patient to use their hospital data. The study was approved by the Ethics committee of Afiyet Hospital. Informed written consent was obtained from the parents/guardians of the children, providing all the necessary information about the study.

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