Article

Neonatal Outcomes of Pregnant Women With Confirmed Coronavirus Disease 2019: One-Year Experience of a Tertiary Care Center

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic became an important public health problem affecting all age groups. The aim of this study was to evaluate clinical and laboratory findings of newborns born to mothers with COVID-19. Thirty pregnant women with COVID-19 were admitted to Turgut Ozal University Hospital for delivery. Fourteen pregnant women had at least one symptom associated with COVID-19. Positive polymerase chain reaction (PCR) results were seen in only 3 (9.7%) of 31 newborns. A statistically significant difference was observed between PCR-positive and PCR-negative newborns in terms of any adverse pregnancy outcomes. Neonatal lymphocyte count and partial arterial oxygen pressure were significantly lower in the PCR-positive group. Results were also compared according to the interval from the maternal diagnosis time to delivery. Hemoglobin and hematocrit levels in newborns born to mothers diagnosed more than 7 days before delivery were significantly lower. Neonates born to mothers with COVID-19 had mild clinical symptoms and favorable outcomes.

Keywords

COVID-19, pregnancy, neonatal outcomes

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) first emerged in China in late 2019 and rapidly became an important public health problem affecting all age groups. Thus far, the virus has infected approximately 240 million people and resulted in 5 million deaths worldwide. It has become clear that this virus has more devastating effects in the elderly, immune-suppressed, and people with certain concomitant diseases. The pregnant population is also susceptible to COVID-19 infection both because of the suppressed cytotoxic activity of lymphocytes due to increased progesterone, decreased lung capacity, and functional residual capacity.[1] In previous studies, it has been showed that COVID-19 infection in the early stages of pregnancy increases the risks of placental hypoperfusion, miscarriage, fetal growth restriction, preterm birth, and even intrauterine death.[2] In a systematic review in which the majority of the participants were pregnant in the third trimester, the course of COVID-19 was shown to resemble that of other populations.[3] In an another large systemic review and meta-analysis comparing pregnancy and neonatal outcomes in the pandemic period with the pre-pandemic period showed a probable decrease due to inability to exclude referral biases in preterm births while the stillbirth rate was the same.[4] In addition, newborns are at risk of active infection via intrauterine transmission through transplacental hematogenous spread or intrapartum transmission after contact with infected maternal secretions during birth or postnatal transmission via droplet infection from infected family members or caregivers.[5] Transplacental transmission is more likely in the last weeks of pregnancy.[6] Moreover, according to the

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reported data from a multicenter study, no confirmed teratogenic effect was found in the fetuses of pregnant women infected at early gestational weeks.[7]

Recommendations on the management of both pregnant women with COVID-19 and their newborns have been constantly updated. Since the beginning of pandemic, the US Centers for Disease Control and Prevention recommends real-time quantitative reverse transcriptase polymerase chain reaction (RT-PCR) testing for all neonates born to mothers with confirmed COVID-19 and delivered within 14 days regardless of whether there are signs of infection.

While the information about the course of COVID-19 in pregnant women and newborns increases daily, we aimed to evaluate the demographic and clinical characteristics of the newborns born to mothers with confirmed COVID-19 within 14 days prior to birth in our institution.

Methods

This was a single-center, retrospective, cross-sectional study, and the approval was obtained from the Ministry of Health and the Local Ethics Committee (Approval Number 2021/67). Maternal-newborn dyads who delivered at Malatya Turgut Ozal University Hospital from March 2020 to March 2021, with a confirmed COVID-19 infection in mothers in the last 14 days before birth, were identified and included to the study. The participants' demographic and clinical data were obtained from hospital records. Symptomatic pregnant women or asymptomatic pregnant women with a positive contact history were tested by using the Bio-Speedy SARS-CoV-2 (2019-nCoV) RT-qPCR detection kit (Bioeksen) and were classified according to the PCR results on nasopharyngeal swab samples.[8] Pregnant women with negative results, both pregnant women and newborns diagnosed using non-PCR methods (such as ELISA), those who had been infected for >14 days before delivery and maternal-newborn dyads who refused to participate were excluded from the study. Delivery timing and method were planned according to obstetric conditions. Maternal age, parity, time of COVID-19 infection diagnosis, presence of COVID-19-related symptoms, body mass index, medical treatments, presence of any adverse pregnancy outcomes including gestational diabetes mellitus, meconium-stained amniotic fluid, preeclampsia, premature rupture of the membranes, and laboratory parameters were recorded. All deliveries were carried out in a preplanned isolated delivery or operating room reserved for pandemic patients only. All health care professionals caring for pregnant women and newborns were protected with full personal protective equipment. While it was recommended that all neonates born to COVID-19-positive mothers were routinely hospitalized for closely monitoring the signs and symptoms due to the unknown course of the disease at the beginning of the pandemic, in parallel with the current literature information, this practice was abandoned and rooming-in procedures were practiced. Combined nasopharyngeal and oropharyngeal swab samples were taken from newborns at 24 and 48 hours. The families were informed about breastfeeding, expressed milk, and formula, and the feeding method decision was left to the parents. Gender, birth weight, Apgar scores, PCR results, diet, presence of symptoms, need for treatment, and laboratory findings including cord blood gas were recorded as newborn data. Asymptomatic newborns who had consecutive negative PCR results were discharged after appropriate hygiene training and ensuring close follow-up. Newborns with positive PCR results were also monitored for signs of infection and were discharged when there are no symptoms and on condition of quarantine at home. The management of pregnant women and newborns was carried out according to the current Ministry of Health guidelines and the recommendations of the Turkish Neonatal Society.[9]

Statistical analyses were performed using IBM SPSS Statistics 26.0. The results are presented as median (min-max) or numbers (n) and percentages. Conformity to the normal distribution was assessed using the Shapiro-Wilk test. For the statistical analyses, the Mann-Whitney U test, independent-samples t test, Pearson χ^2 test, and Fisher's exact test were used. A P value $<.05$ was considered statistically significant.

Results

During the study period, 30 pregnant women with confirmed COVID-19 were hospitalized for delivery. Only one patient (3.3%) had twin pregnancy, and 70% were multiparous. The mean gestational age at COVID-19 diagnosis and at delivery were 38 ± 2 and 39 ± 1 weeks, respectively. The neonates' mean birth weight was 3282 ± 461 g. The rate of spontaneous preterm birth before 37 weeks was 10% ($n = 3$). The pregnant women's mean body mass index was 28.1 ± 4.9. By ethnicity, all of the pregnant women were Turkish except for only one Syrian immigrant woman. None of the mothers were vaccinated against SARS-CoV-2, and none of them smoked during pregnancy. The majority of pregnant women (60%) did not have an adverse pregnancy outcome; of the remaining 12 women, 6 had gestational diabetes mellitus, 3 had meconium-stained amniotic fluid, 2 had preeclampsia, and 1 had premature rupture of membranes. Fourteen pregnant women (46.7%) had

at least one symptom related to COVID-19, and 16 were asymptomatic. The main symptoms related to COVID-19 reflected the effects of the virus on the respiratory tract. The most common symptom was cough (40%), followed by loss of smell/taste and fever (each 26.7%), fatigue/malaise (20%), and sore throat/rhinorrhea (16.7%). None of the pregnant women received specific medical treatment for COVID-19 before delivery. Only one patient was treated with per oral hydroxychloroquine after delivery for 1 week and then had full recovery. Moreover, none of the pregnant women developed severe COVID-19 pneumonia/disease requiring respiratory support or intensive care unit admission.

Only 3 of 31 newborns (9.7%) had positive PCR results, and all of them were term babies. Two of them were positive in the first 24 hours, while the other was positive at 48th hour. Our study demonstrated a statistically significant difference between PCR-positive and PCR-negative infants in terms of any adverse pregnancy outcome ($P < .05$). In addition, the neonatal lymphocyte count and cord blood partial arterial oxygen pressure were significantly lower in the PCR-positive infant group ($P < .05$ and $P < .001$, respectively). The results also indicated that there was no significant relationship between infants' PCR results and maternal obesity, presence of any maternal COVID-19 symptom, mode of delivery, or feeding type. Clinical and laboratory characteristics of participants according to whether newborns had positive PCR tests are summarized in Table 1. Newborns with positive PCR tests showed no respiratory or other systemic symptoms and no radiological findings related to COVID-19; none of them received specific treatment. There was no need for continuous positive airway pressure or mechanical ventilation except for a short-term oxygen requirement during the transition period. Furthermore, the newborns in the PCR-negative group had early neonatal periods without any problems.

We also compared the newborns' results according to when their mothers were diagnosed with COVID-19. We found that the hemoglobin and hematocrit levels of newborns born to mothers diagnosed more than 7 days before delivery were significantly lower ($P < .05$) than those of infants born to mothers diagnosed at 8 to 14 days prior to birth. Clinical and laboratory characteristics of newborns according to mothers' time of diagnosis are summarized in Table 2.

Fortunately, no maternal or neonatal death was observed in the present study.

Discussion

In this study, we assessed the demographic and clinical characteristics of newborns born to mothers with confirmed COVID-19 and compared the neonatal outcomes according to the time of the mothers' diagnosis and the neonatal PCR results. Consistent with previous studies, the results of this study showed that neonates born to mothers with COVID-19 had mild clinical symptoms and favorable outcomes.

There has been a rapid increase in knowledge about impacts of the SARS-CoV-2 virus on pregnant women and their newborns. In the present study, 46.7% of pregnant women had at least one symptom associated with COVID-19, the most common being cough, fever, and loss of smell/taste. Previous studies have shown that pregnant women with COVID-19 exhibited clinical characteristics similar to those of nonpregnant women.[10] In a review including 33 studies covering 385 pregnant women, 95.6% of pregnant women had a "mild" infection course.[11] However, the results of a meta-analysis documenting 5560 pregnant women suggested that COVID-19 pneumonia was more common in pregnant than in nonpregnant women.[12] In another study from Turkey, 75% of pregnant women participants were symptomatic and similar to the symptom ranking in our results, they also found that cough (62.5%) and fever (54.1%) were the most common symptoms during COVID-19 infection.[13]

The results of this study showed that the rate of premature birth in pregnant women with confirmed COVID-19 was 10%. Similarly, in a study conducted with the early data in China, the premature birth rate was found to be 12.1%, and in the same study, PCR positivity in newborns was reported as 9%, similar to our results.[14] However in a multi-center study in Spain of pregnant women who delivered within 14 days after a COVID-19 diagnosis, the prematurity rate was 30.5%.[15] The PregCOV-19 Living Systematic Review reported the preterm birth risk was 17% and suggested that majority (94%) of which were iatrogenic.[16] This difference in preterm delivery rates can be attributed to the maternal disease severity. Mullins et al revealed that preterm delivery occurred in a higher proportion of women with SARS-CoV-2 infection and suggested that health care providers should recommend SARS-CoV-2 vaccination in pregnant women in their co-reporting of common outcomes from PAN-COVID and AAP-SONPM registries.[17] All newborns in the present study were of appropriate size for their gestational age. In contrast, Verma et al reported that SARS-CoV-2 infection in their cohorts resulted in a prevalence of 10% of newborns who were small for gestational age.[18] This difference in results may be due to the fact that our study was only conducted on patients in late pregnancy. Therefore, birth weights may not be affected by the mother's acute infection process.

The data presented in this study identified a 9.7% PCR positivity rate in neonates. Consistent with our

Table 1. Clinical and Laboratory Characteristics of COVID-19-Positive Pregnant and Newborn Dyads According to Neonatal SARS-CoV-2 PCR Positivity[a].

Characteristics	Newborns with SARS-CoV-2 (N = 3)	Newborns without SARS-CoV-2 (N = 28)	*P*
Gestational age at delivery, weeks	39 (38-40)	39 (36-40)	.68
Birth weight, grams	3100 (2840-3460)	3400 (2530-4160)	.54
Parity, multiparous	2 (67.7)	19 (67.9)	1.00
Mode of delivery, CS	1 (33.3)	15 (53.6)	.60
Gender, male	0 (0)	16 (57.1)	.10
Prematurity, <37 weeks	0 (0)	3 (10.7)	1.00
Apgar at 1 minute	9 (8-9)	9 (5-10)	.54
Apgar at 5 minutes	10 (9-10)	10 (6-10)	.59
Type of feeding, formula	3 (100)	17 (60.7)	.53
Adverse pregnancy outcome			**.04**[b]
None	0 (0)	19 (67.9)	
PROM	0 (0)	1 (3.6)	
GDM	2 (66.7)	4 (14.3)	
MSAF	0 (0)	3 (10.7)	
PE	1 (33.3)	1 (3.6)	
Any maternal COVID-19 symptom	1 (33.3)	13 (46.4)	1.00
Obesity, BMI ≥30 kg/m^2	2 (66.7)	7 (25)	.19
Maternal laboratory tests			
Hemoglobin, g/dL	12.3 (8.9-13.3)	12.2 (9.4-15.5)	.63
WBC count, /μL	10540 (5930-15180)	8040 (5230-17890)	.63
Neutrophil count, /μL	6960 (3940-12420)	6020 (3310-17000)	.59
Lymphocyte count, /μL	1680 (1620-2910)	1535 (280-3360)	.28
Platelets, ×10^3/μL	275 (182-500)	209.5 (131-424)	.25
CRP, mg/dL	0.34 (0.02-0.65)	1.44 (0.02-21.14)	.14
AST, U/L	31 (30-40)	25 (13-97)	.35
ALT, U/L	15 (13-16)	15.5 (6-121)	.92
PT, seconds	10.6 (10.4-11)	10.5 (9.2-12.2)	.50
aPTT, seconds	28.2 (27.1-31.5)	27.6 (22.3-32.5)	.38
INR	0.97 (0.96-1.08)	0.99 (0.88-1.1)	.97
Neonatal laboratory tests			
Hemoglobin, g/dL	17.7 (14.3-20.8)	17.2 (14.7-22.4)	.92
WBC count, /μL	16840 (8920-17440)	14060 (8110-28170)	.82
Neutrophil count, /μL	9540 (5350-11670)	7005 (2130-20940)	.50
Lymphocyte count, /μL	2950 (2390-4160)	5010 (2020-10890)	**.03**[b]
Platelets, ×10^3/μL	364 (148-366)	284 (142-421)	.53
CRP, mg/dL	0.24 (0.02-0.72)	0.02 (0.02-2.26)	.16
Cord blood gas values			
pH	7.37 (7.21-7.37)	7.34 (7.20-7.45)	.77
pO_2, mm Hg	29.9 (27.2-30)	48.3 (32.9-74.6)	**.0001**[b]
pCO_2, mm Hg	45.6 (44.2-50.2)	41.9 (25.2-58)	.28
Base deficit, mmol/L	1.5 (1.3-6.8)	3.6 (0.5-9.2)	.42
Bicarbonate, mmol/L	23.3 (19.7-23.9)	21.2 (16.3-23.9)	.31
Hospitalization, days	6 (4-7)	2 (1-5)	**.01**[b]

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; CS, cesarean section; PROM, premature rupture of the membranes; GDM, gestational diabetes mellitus; MSAF, meconium-stained amniotic fluid; PE, preeclampsia; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; AST, aspartate aminotransferase; ALT; alanine aminotransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

[a]Data presented as median (min-max) and n (%).

[b]Bold values indicate significant values at the level of $P < .05$.

Table 2. Comparison of Neonatal Outcomes According to Maternal Diagnosis Time Before Delivery[a].

	0-7 days before delivery (N = 16)	8-14 days before delivery (N = 14)	*P*
PCR positivity	2 (93.8)	1 (6.7)	1.00
Prematurity, <37 weeks	—	3 (21.4)	1.00
Apgar 1	9 (5-10)	9 (7-9)	.80
Apgar 5	10 (6-10)	10 (8-10)	.59
Resuscitation in the delivery room	1 (6.2)	1 (7.1)	1.00
pH	7.35 (7.20-7.43)	7.35 (7.21-7.45)	.80
pO_2, mm Hg	45.7 (29.9-67.5)	49.9 (27.2-74.6)	.33
pCO_2, mm Hg	44.7 (25.2-58)	41.4 (26.4-50.4)	.35
Base deficit, mmol/L	3.4 (0.8-9.2)	3.5 (0.5-8.8)	.57
Bicarbonate, mmol/L	20.3 (16.3-23.9)	21.7 (17.5-23.9)	.65
Lactate, mmol/L	4.2 (2.4-8)	3.4 (1.7-8)	.14
Hemoglobin, g/dL	17.9 (16.6-22.4)	15.6 (14.3-18.8)	**.003**[b]
Hematocrit, %	51.9 (48.4-65.6)	47.3 (40.7-57.2)	**.012**[b]
WBC count, /μL	15610 (8110-23910)	12070 (9850-28170)	.35
Neutrophil count, /μL	8440 (4920-16700)	5250 (2130-20940)	.05
Lymphocyte count, /μL	4185 (2020-7110)	5020 (2950-10890)	.28
Platelets, $\times 10^3$/μL	275.5 (142-364)	325 (158-421)	.07
CRP, mg/dL	0.02 (0.02-0.81)	0.02 (0.02-2.26)	.65

Abbreviations: PCR, polymerase chain reaction; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; WBC, white blood cell; CRP, C-reactive protein.
[a]Data presented as median (min-max) and n (%).
[b]Bold values indicate significant values at the level of $P < .05$.

result, Zeng et al found this rate to be 9% in their cohort study in Wuhan, where the pandemic first appeared.[14] In another report involving participants similar to our study population, the percentage of PCR positivity was found to be 4.3% among infants of mothers identified in the last 14 days before delivery.[19] In a single-center study conducted in India, 32 out of 221 newborns born to mothers with COVID-19 were positive (14.47%).[20] However, neonatal infection was reported in 1% to 3% of births to US mothers with COVID-19, with decreasing rates as the mother's diagnosis time goes back especially more than 14 days.[19,21] We consider that this variety in positivity rates may depend on heterogeneity of sample sizes and maternal diagnosis time but it also varies from country to country. In this study, none of the newborns developed symptoms regardless of PCR positivity. In line with our results, a retrospective national study that included 185 pregnant women infected by SARS-CoV-2 and the 167 neonates born to them found that most of the newborns were asymptomatic.[22] Again, in a meta-analysis that included 32 studies and 261 newborns born to mothers with SARS-CoV-2 infection, it was revealed that most of the neonates (80.4%) did not show any clinical abnormalities.[23] Our study also showed that there was no statistically significant relationship between presence of any maternal COVID-19 symptoms, maternal obesity, mode of delivery, and neonatal PCR results. In line with our results, Verma et al classified mothers as symptomatic or asymptomatic and evaluated neonatal outcomes but found no relationship in terms of newborn PCR positivity.[18] Similar to our results, Anand et al also failed to show any correlation between symptomatic mothers and neonatal PCR positivity.[24] Furthermore, in a multicenter cohort study investigating the clinical and sociodemographic factors affecting neonatal test result positivity, no association was found with vaginal delivery and maternal symptomatic COVID-19 disease and only maternal social vulnerability was the main risk factor.[25] In our study, we also examined the relationship between the time of diagnosis of the mother and neonatal PCR positivity, but we could not find a significant relationship. Consistent with our result, Oncel et al found that there was no statistically significant relationship between the interval between maternal symptoms and delivery and neonatal PCR positivity.[26] At this point, it can be speculated that due to the low incidence of neonatal PCR positivity, it is challenging to identify the risk factors.

Laboratory evidence of infected newborns are usually nonspecific. Patients may have leukocytosis, lymphopenia, mild thrombocytopenia, and elevated inflammatory markers.[27] In our study, we found only the number of lymphocytes were lower in PCR-positive newborns compared with PCR-negative group when

analyzed with hemogram parameters and C-reactive protein levels. On the other hand, Oncel et al found that the neutrophil count was statistically lower in newborns with SARS-CoV-2.[26] In a review of the laboratory findings of COVID-19 infection in different age groups and pregnant women, especially for the newborn period, it was emphasized that generally normal C-reactive protein levels and very different and conflicting laboratory results regardless of clinical symptoms.[28] We also evaluated the cord blood gas values of newborns and showed that partial arterial oxygen pressure values of PCR-positive newborns were significantly lower than those of PCR-negative infants ($P < .001$). Another remarkable finding was the significantly higher hemoglobin and hematocrit levels in newborns whose mothers were diagnosed within 0 to 7 days before birth ($P < .05$). Although we could not confirm through placental pathology, we attribute this result to increased fetal erythropoiesis triggered by placental hypoxia due to acute infection. Limited data exist to date on the detailed laboratory findings in newborns with COVID-19; therefore, we think that our study contributes the literature in this context.

In our study, we found that more parents decide to employ formula feeding over expressed breast milk, but we did not find a statistical relationship between PCR positivity and feeding method. We attribute this preference to families' fear of virus transmission. To date, there is no clear evidence that SARS-CoV-2 virus is transmitted from an infected mother to her neonate via breast milk.[29] Furthermore, breast milk has a unique structure. Given the protective antibodies and other bioactive components it contains, breast milk may carry an additional benefit when babies are born to mothers with COVID-19. UNICEF and the World Health Organization recommend the continuation of breastfeeding in compliance with appropriate respiratory and hand hygiene during COVID-19 infection.[30,31] In our institution, this recommendation was followed case by case and in agreement with the parents' decision. In this regard, we believe that mothers should be given more intense breastfeeding counselling as soon as COVID-19 is diagnosed prenatally.

This study has noticeable strengths in presenting detailed data about demographic and clinical characteristics of maternal and newborn dyads, including cord blood gas parameters. Furthermore, we also compared newborns according to both PCR results and the time of mothers' diagnosis. On the other hand, our study has several limitations. First, our study had a retrospective design; second, the results of our study reflect only a short period of late gestation in pregnant women and only the early neonatal period in infants and finally small subject number.

In conclusion, based on the results of the present study, maternal and early neonatal outcomes are favorable for pregnant women diagnosed with COVID-19 in the last 14 days before birth. Considering the clinical variety of the infection, further studies are needed to more clearly define the early and late neonatal outcomes and the risk factors.

Authors' Note

The English in this document was checked by at least two professional editors, both native speakers of English. For a certificate, please see http://www.textcheck.com/certificate/LwILVP.

Author Contributions

NAM: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
HO: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SY: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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