Original Investigation | Özgün Araştırma

Gazi Med J 2026;37(3):376-383

DOI: http://dx.doi.org/10.12996/gmj.2026.4641

Neonatal Outcomes in Infants Born to Mothers Recovered from COVID-19 During Pregnancy: A Single-Center Experience in Türkiye's Level IV NICU

Gebelikte COVID-19 Geçiren Annelerden Doğan Bebeklerde Yenidoğan Sonuçları: Türkiye'de Düzey IV Yenidoğan Yoğun Bakım Ünitesinin Tek Merkez Deneyimi

Elif Keleş[1,2], Gizem Kartal[1,3], Melda Taş[1,4], Münevver Baş[1,5], Nurcan Hanedan[1,6], Ayfer Koyuncu[7], İbrahim Murat Hırfanoğlu[1], Esra Önal[1], Canan Türkyılmaz[1], Ebru Ergenekon[1], Esin Koç[1]

[1]Division of Neonatology, Department of Pediatrics, Gazi University, Faculty of Medicine, Ankara, Türkiye
[2]Department of Radiology, Northwestern University, Hybrid and Machine Intelligence Lab, Chicago, United States of America
[3]Clinic of Pediatrics, University of Health Sciences Türkiye, Gaziantep City Hospital, Gaziantep, Türkiye
[4]Clinic of Pediatrics, University of Health Sciences Türkiye, Ankara Training and Research Hospital, Ankara, Türkiye
[5]Clinic of Pediatrics, University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital, Balıkesir, Türkiye
[6]Clinic of Pediatrics, University of Health Sciences Türkiye, Ankara Etlik City Hospital, Ankara, Türkiye
[7]Department of Biomedical Engineering, Düzce University, Faculty of Medicine, Düzce, Türkiye

ABSTRACT

Objective: The impact of in utero exposure to maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on neonatal health, particularly in the absence of active infection at delivery, remains incompletely understood. This study evaluated early neonatal outcomes and short-term follow-up among infants exposed to maternal Coronavirus Disease-2019 (COVID-19) during pregnancy, compared with unexposed neonates.

Methods: This retrospective observational cohort study was conducted at Gazi University Faculty of Medicine Hospital, a tertiary university hospital with a Level IV NICU, between March 2020 and August 2021. Neonates who tested polymerase chain reaction (PCR)-negative at delivery and were born to mothers with PCR-confirmed SARS-CoV-2 infection during pregnancy were classified as exposed, while neonates born to mothers without a history of COVID-19 during pregnancy served as controls. Neonatal outcomes during hospitalization and at one-month follow-up were assessed.

Results: A total of 196 neonates were included, of whom 112 were exposed in utero to maternal COVID-19. Neonatal intensive care unit (NICU) admission was more frequent among exposed infants [28.4%

ÖZ

Amaç: Gebelik sırasında maternal şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2) enfeksiyonuna intrauterin maruziyetin yenidoğan sağlığı üzerindeki etkileri, özellikle doğum sırasında aktif enfeksiyon bulunmayan olgularda, tam olarak açıklığa kavuşmamıştır. Bu çalışmada, gebelik sırasında koronavirüs hastalığı-2019 (COVID-19) geçiren annelerden doğan ve doğumda polimeraz zincir reaksiyonu (PCR) testi negatif olan bebeklerin erken yenidoğan dönem sonuçları ve kısa dönem izlemleri, maruziyeti olmayan yenidoğanlarla karşılaştırılarak değerlendirilmiştir.

Yöntemler: Bu retrospektif gözlemsel kohort çalışması, Mart 2020 ile Ağustos 2021 tarihleri arasında üçüncü basamak bir üniversite hastanesinde gerçekleştirildi. Gebelik sırasında PCR ile doğrulanmış SARS-CoV-2 enfeksiyonu geçiren ve doğum sırasında PCR testi negatif olan annelerden doğan bebekler maruz kalan grup olarak tanımlandı. Gebelik sırasında COVID-19 öyküsü bulunmayan annelerden doğan yenidoğanlar ise kontrol grubunu oluşturdu. Hastanede yatış süresince ve yaşamın ilk ayında yenidoğan sonuçları değerlendirildi.

Bulgular: Çalışmaya toplam 196 yenidoğan dahil edildi ve bunların 112'si maternal COVID-19 enfeksiyonuna intrauterin maruz kalmıştı.

Cite this article as: Keles E, Kartal G, Tas M, Baş M, Hanedan N, Koyuncu A, et al. Neonatal outcomes in infants born to mothers recovered from COVID-19 during pregnancy: a single-center experience in Türkiye's level IV NICU. Gazi Med J. 2026;37(3):376-383

Address for Correspondence/Yazışma Adresi: Elif Keleş, Department of Pediatrics, Division of Neonatology, Gazi University Faculty of Medicine, Ankara, Türkiye; Department of Radiology, Northwestern University, Hybrid and Machine Intelligence Lab, Chicago, United States of America
E-mail / E-posta: elif.keles@northwestern.edu
ORCID ID: orcid.org/0000-0001-8103-797X

Received/Geliş Tarihi: 13.02.2026
Accepted/Kabul Tarihi: 20.05.2026
Publication Date/Yayınlanma Tarihi: 10.07.2026

ABSTRACT

vs. 11.9%; relative risk (RR): 2.38, 95% confidence interval (CI): 1.25-4.54; p = 0.007]. In exposed neonates, hyperbilirubinemia requiring phototherapy occurred more frequently (38.8% vs. 22.2%; RR: 1.75, 95% CI: 1.08-2.85; p = 0.017), and the onset of jaundice occurred earlier [median (interquartile range) 3 (2-3) vs. 5.5 (3-8) days; p = 0.006]. Direct Coombs testing (performed in a clinically selected subset) showed similar overall positivity rates, but high-grade positivity (≥2+) occurred exclusively among exposed infants (p = 0.004). In trimester-specific analyses, second-trimester maternal infection was associated with a higher rate of neonatal endotracheal intubation than with first- or third-trimester exposure (10.0% vs. 0%; p = 0.034). No group differences were observed in early postnatal complications or rehospitalizations at one month.

CONCLUSION: Resolved maternal SARS-CoV-2 infection during pregnancy was not associated with major adverse neonatal outcomes, but it was linked to more frequent NICU admissions, earlier onset of clinical jaundice, a higher incidence of hyperbilirubinemia requiring treatment, and distinct patterns of severity on the direct Coombs test, potentially consistent with altered immune or hematologic processes. A trimester-specific association with endotracheal intubation was observed and should be interpreted cautiously.

Keywords: COVID-19, maternal SARS-CoV-2 infection, neonatal outcomes, hyperbilirubinemia, immune reaction, exposed neonate

ÖZ

Yenidoğan yoğun bakım ünitesine (YYBÜ) yatış oranı maruz kalan bebeklerde daha yüksekti [%28,4'e karşı %11,9; göreceli risk (RR): 2,38; %95 güven aralığı (GA): 1,25-4,54; p = 0,007]. Fototerapi gerektiren hiperbilirubinemi maruz kalan grupta daha sık görüldü (%38,8'e karşı %22,2; RR: 1,75; %95 GA: 1,08-2,85; p = 0,017) ve sarılık daha erken dönemde ortaya çıktı [medyan (çeyrekler arası aralık) 3 (2-3) güne karşı 5,5 (3-8) gün; p = 0,006]. Direkt Coombs testi pozitiflik oranları benzer olmakla birlikte, yüksek dereceli pozitiflik (≥2+) yalnızca maruz kalan bebeklerde saptandı (p = 0,004). Trimester bazlı analizlerde, ikinci trimesterde maternal enfeksiyon geçiren annelerin bebeklerinde endotrakeal entübasyon oranı birinci ve üçüncü trimester maruziyetine göre daha yüksekti (%10,0'a karşı %0; p = 0,034). Erken postnatal komplikasyonlar ve bir aylık yeniden hastaneye yatış oranları açısından gruplar arasında anlamlı fark bulunmadı.

Sonuç: Gebelik sırasında geçirilmiş ve doğum öncesinde düzelmiş maternal SARS-CoV-2 enfeksiyonu majör olumsuz yenidoğan sonuçları ile ilişkili bulunmamıştır. Bununla birlikte, daha sık YYBÜ yatışı, sarılığın daha erken başlaması, tedavi gerektiren hiperbilirubinemi sıklığında artış ve direkt Coombs testinde farklı şiddet paternleri ile ilişkili olduğu gösterilmiştir. Ayrıca ikinci trimester maruziyeti ile endotrakeal entübasyon arasında gözlenen ilişki dikkatle yorumlanmalıdır.

Anahtar Sözcükler: COVID-19, maternal SARS-CoV-2 enfeksiyonu, yenidoğan sonuçları, hiperbilirubinemi, immün yanıt, maruz kalan yenidoğan

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) pandemic challenged global health systems, particularly for pregnant individuals, who are considered an especially vulnerable population (1). Physiological adaptations of pregnancy, including significant changes in the immune, cardiovascular, and respiratory systems, may increase susceptibility and disease severity (2). These considerations raised concerns about potential maternal, fetal, and neonatal consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy.

During the pandemic, initial clinical focus centered on the possibility of vertical transmission. Evidence demonstrates that transplacental transmission of SARS-CoV-2 is rare, and neonatal infection occurs in only a minority of exposed infants (1,3). As a result, the clinical question has shifted toward the potential indirect effects of maternal infection on the intrauterine environment and neonatal health, even in the absence of direct viral transmission (1,3,4).

Large cohort studies and systematic reviews have demonstrated that maternal SARS-CoV-2 infection during pregnancy is associated with increased risks of adverse perinatal outcomes, including preeclampsia, preterm birth, neonatal respiratory morbidity, stillbirth, and higher rates of neonatal intensive care unit (NICU) admission, particularly among women with severe or symptomatic disease (5-7). However, how resolved maternal infection affects neonatal health remains unclear. Existing studies have yielded diverging results due to variations in disease severity, exposure timing, population characteristics, and study design. Consequently, whether in utero exposure to maternal COVID-19 presents neonatal risk in the absence of active maternal infection at delivery remains an important unanswered clinical question (3,5-7).

Although the global epidemiology of COVID-19 has evolved, SARS-CoV-2 continues to circulate, and a substantial number of pregnancies worldwide have been affected (8,9). Declining vaccination coverage in pregnancy further underscores the ongoing clinical importance of characterizing neonatal outcomes in this context (8). Such understanding has direct relevance for postnatal monitoring strategies and counseling of affected families (10-12).

Our study aimed to evaluate early neonatal outcomes and one-month follow-up among infants born to mothers with documented SARS-CoV-2 infection during pregnancy who tested polymerase chain reaction (PCR)-negative at delivery, and to compare these outcomes with those of unexposed neonates. We assessed birth anthropometrics, early neonatal morbidity, postnatal adaptation, and short-term clinical outcomes to determine whether resolved maternal COVID-19 is associated with risks to neonatal health.

MATERIALS AND METHODS

This retrospective observational cohort study included 196 neonates born at Gazi University Faculty of Medicine Hospital that has a level IV NICU between March 2020 and August 2021. The study population comprised neonates who required NICU admission and those who remained with their mothers and were followed in the postnatal maternal ward.

The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Clinical Research Ethics Committee, approval number 497, date 31.05.2021, and the requirement for informed consent was waived because of the study's retrospective nature.

Neonates were classified as unexposed if they were born to mothers who had no documented history of SARS-CoV-2 infection during pregnancy and who tested PCR-negative at delivery. The exposed

group consisted of infants born to mothers with confirmed SARS-CoV-2 infection during pregnancy [diagnosed by reverse transcription (RT)-PCR of nasopharyngeal swabs] whose infection had resolved by delivery, as confirmed by negative RT-PCR testing. Mothers with active infection at delivery (positive RT-PCR) were excluded. None of the mothers in either group had received COVID-19 vaccination, as vaccines were not available or were restricted by priority policies during the study period.

Clinical and demographic data were systematically extracted from electronic medical records. Maternal variables included gravidity, parity, history of preterm labor, and comorbid conditions such as gestational diabetes mellitus, hypertensive disorders of pregnancy, hypothyroidism, and smoking status. Maternal COVID-19-related data included trimester of infection, symptom severity, pharmacologic treatment history, and prenatal fetal evaluations, including routine ultrasound examinations and fetal echocardiography when available.

Perinatal and neonatal data included gestational age at birth, birth weight, length, head circumference, and their corresponding percentile values based on standard growth charts. Apgar scores at 1 and 5 minutes, the need for delivery-room resuscitation (including positive-pressure ventilation), NICU admission, respiratory support requirements [supplemental oxygen, continuous positive airway pressure (CPAP), or invasive mechanical ventilation], and NICU course and duration were recorded.

Neonatal clinical course variables included primary admission diagnosis, timing of hyperbilirubinemia onset, initiation of phototherapy, presence of intrauterine growth restriction, antibiotic therapy, inotropic support, and laboratory parameters, when available, including complete blood count, C-reactive protein, and interleukin-6. All neonatal complications occurring within the first four weeks of life were documented to assess early postnatal outcomes.

Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, and the Fisher-Freeman-Halton exact test was applied for trimester-based analyses. The normality of continuous variables was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test, and the homogeneity of variances was evaluated using Levene's test. Parametric tests (independent-samples t-test or one-way analysis of variance with Tukey post-hoc test) were used when assumptions were met; otherwise, non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test) were applied. Continuous data are presented as mean ± standard deviation or median [interquartile range (IQR)], as appropriate (13,14).

For trimester-specific analyses with sparse data or zero-event cells, exact methods were employed, including the Freeman-Halton extension of Fisher's exact test with Monte Carlo simulation (100,000 resamples). Relative risks (RR) with corresponding 95% confidence intervals (CIs) were calculated for key clinical outcomes, including NICU admission and hyperbilirubinemia (15).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (version 29.0; IBM Corp., Armonk, NY). A two-sided p-value was considered statistically significant.

RESULTS

A total of 196 neonates were included: 112 (57.1%) were classified as exposed, born to mothers who had documented SARS-CoV-2 infection during pregnancy but who tested PCR-negative at delivery, and 84 (42.9%) were unexposed, born to mothers with no history of SARS-CoV-2 infection during pregnancy.

Baseline maternal and obstetric characteristics were comparable between groups (Tables 1 and 2). Mean maternal age was 30 ± 5 years in both cohorts (p = 0.68). Gravidity, parity, number of living children, and gestational age at delivery did not differ significantly between groups (all p > 0.05; Supplementary Table 1). Gestational ages were predominantly clustered at term, with a median of 38 weeks (IQR: 37-39; range 29+3 to 41+0). Preterm birth (<37 weeks) occurred in 21 of 112 infants (18.8%) with in utero SARS-CoV-2 exposure and in 10 of 84 unexposed infants (11.9%), with no statistically significant difference between groups (p = 0.19). Early preterm birth (<34 weeks) was uncommon in both groups (5.4% vs. 2.4%, p = 0.47). Among exposed mothers, SARS-CoV-2 infection occurred in the first, second, and third trimesters in 22 (19.6%), 45 (40.2%), and 45 (40.2%), respectively. Fourteen mothers (12.5%) were symptomatic during infection, most commonly with fever and cough, and six (5.4%) received pharmacologic treatment. Maternal characteristics and key neonatal outcomes by exposure status are summarized in Table 1.

Maternal comorbidities, pregnancy characteristics, antenatal screening results, and mode of delivery were similar between the exposed and unexposed groups (all p > 0.05) (Table 1).

Neonatal anthropometric measurements at birth and growth percentiles did not differ significantly between groups (Table 2). Apgar scores at 1 and 5 minutes did not differ significantly between infants born to COVID-19-exposed mothers and unexposed controls (p > 0.05). Intrauterine growth restriction was not significantly associated with maternal COVID-19 infection during pregnancy (p = 0.17).

Although delivery room positive-pressure ventilation was more frequently required in exposed infants (7.3% vs. 2.4%), this difference did not reach statistical significance (p > 0.05) (Table 3). NICU admission occurred more frequently among exposed infants compared with unexposed infants [28.4% vs. 11.9%, p = 0.007; RR 2.38, 95% CI: 1.25-4.54] (Table 1). The distribution of indications for NICU admission by exposure status is presented in Table 4. Among admitted infants, rates of respiratory support (CPAP, intubation), resuscitation, antibiotics, and vasoactive support did not differ (all p > 0.05) (Table 3).

Admission indications (tachypnea, hyperbilirubinemia, and prematurity) were similarly distributed between groups (p > 0.05; Table 4). Analysis of a subset of infants revealed no significant differences in length of NICU stay or in postnatal inflammatory markers between the COVID-19-exposed and -unexposed groups (p > 0.05) (Supplementary Table 2).

Hyperbilirubinemia requiring treatment was more frequent among exposed infants (38.8% vs. 22.2%, p = 0.017; RR: 1.75, 95% CI: 1.08-2.85) (Table 3). In addition, the onset of jaundice occurred earlier in exposed infants [median 3 days (IQR 2-3)] than in unexposed controls [median 5.5 days (IQR 3-8), p = 0.006], whereas peak total

Table 1. Maternal and neonatal outcomes according to in utero SARS-CoV-2 exposure.

Variable	Exposed (n = 112)	Unexposed (n = 84)	p-value	RR (95% CI)
Maternal characteristics				
Gestational diabetes mellitus	16 (14.4%)	12 (14.3%)	0.99	
Hypothyroidism	24 (21.4%)	20 (23.8%)	0.68	
Hypertension	5 (4.5%)	5 (6.0%)	0.64	
Preeclampsia	3 (2.7%)	4 (4.8%)	0.46	
Smoking	8 (7.1%)	6 (7.1%)	0.99	
Cesarean delivery	88 (79.3%)	62 (74.7%)	0.44	
Antenatal steroids	14 (12.5%)	17 (20.2%)	0.14	
IVF pregnancy	16 (14.8%)	8 (9.6%)	0.27	
Neonatal outcomes				
Preterm birth (<37 weeks)	21 (18.8%)	10 (11.9%)	0.19	1.57 (0.80–3.08)
Early preterm (<34 weeks)	6 (5.4%)	2 (2.4%)	0.47	2.25 (0.47–10.7)
Positive-pressure ventilation	8 (7.3%)	2 (2.4%)	1.00	3.00 (0.66–13.6)
CPAP support	4 (3.8%)	3 (3.8%)	0.70	1.00 (0.23–4.29)
Endotracheal intubation	4 (3.8%)	2 (2.5%)	0.70	1.50 (0.29–7.65)
Antibiotic requirement	9 (9.2%)	3 (4.3%)	0.21	2.25 (0.64–7.87)
NICU admission	31 (28.4%)	10 (11.9%)	0.007	2.38 (1.25–4.54)
Hyperbilirubinemia	38 (38.8%)	18 (22.2%)	0.017	1.75 (1.08–2.85)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RR: Relative risk, CI: Confidence interval, IVF: *In vitro* fertilization, CPAP: Continuous positive airway pressure, NICU: Neonatal intensive care unit.

Table 2. Key neonatal clinical outcomes according to in utero COVID-19 exposure.

Variable	Exposed n (IQR range)	Unexposed n (IQR range)	p-value
Birth weight (g)	3090 (2805–3510)	3188 (2925–3455)	0.31
Apgar score (1 min)	9 (8–9)	9 (9–9)	0.91
Apgar score (5 min)	9 (9–10)	9 (9–10)	0.23
NICU stay (days)	3 (1–7)	5 (2–8)	0.30
Day of jaundice onset	3 (2–3)	5.5 (3–8)	0.006
Phototherapy treatment threshold	18.0 [15.6–18.2]	15 18.0 [17.0–18.9]	0.58
Day regained birth weight	8 (6–11)	8 (6–10)	0.50
Day full enteral feeding	1 (1–1)	1 (1–1)	0.06

Data are presented as median (IQR). COVID-19: Coronavirus Disease-2019, IQR: Interquartile range, NICU: Neonatal intensive care unit.

Table 3. Neonatal respiratory and clinical outcomes.

Outcome	Exposed n (%)	Unexposed n (%)	p-value	RR (95% CI)
CPAP support	4 (3.8)	3 (3.8)	>0.05	
Endotracheal intubation	4 (3.8)	2 (2.5)		
Positive-pressure ventilation	8 (7.3)	2 (2.4)		
Antibiotic requirement	9 (9.2)	3 (4.3)		
NICU admission	31 (28.4)	10 (11.9)	0.007	2.38 (1.25–4.54)
Hyperbilirubinemia	38 (38.8)	18 (22.2)	0.017	1.75 (1.08–2.85)

RR: Relative risk, CI: Confidence interval, CPAP: Continuous positive airway pressure, NICU: Neonatal intensive care unit.

bilirubin levels did not differ significantly between groups (Table 2).

Direct Coombs testing was available for a subset of the cohort (n = 57) and was performed when clinically indicated. While the overall prevalence of Coombs positivity did not differ significantly between groups, the distribution of the severity of positivity varied by exposure status. All cases of high-grade (≥2+) Coombs positivity occurred in the exposed group, whereas moderate positivity (1-2+) was more frequent among unexposed infants (p = 0.004) (Table 5). In trimester-specific analyses of exposed infants, the frequency of endotracheal intubation varied by trimester. Infants exposed during the second trimester had a higher rate of intubation (10.0%) compared with infants exposed in the first or third trimesters, in which no intubations were observed (p = 0.034) (Table 6). This signal was not accompanied by consistent differences in related respiratory endpoints (e.g., CPAP or combined respiratory support) or in non-respiratory outcomes. Second-trimester exposure was associated with an increased risk of endotracheal intubation compared with first- and third-trimester exposure combined (RR: 5.2, 95% CI: 1.1-24.6; p = 0.034). Duration-based analyses showed a significant difference in intubation duration across trimesters (Kruskal-Wallis p = 0.036), driven by longer intubation durations among infants exposed in the second trimester.

Feeding progression, postnatal weight loss, time to regain birth weight, achievement of full enteral feeding, and early postnatal complications within the first four weeks of life did not differ significantly between exposed and unexposed infants (all p > 0.05).

Table 4. Indications for NICU admission according to exposure status.

Indication	Exposed (n = 31)	Unexposed (n = 10)	p-value
Tachypnea/respiratory distress	12 (38.7%)	4 (40.0%)	0.93
Hyperbilirubinemia	10 (32.3%)	3 (30.0%)	0.88
Prematurity	7 (22.6%)	2 (20.0%)	0.85
Other	2 (6.4%)	1 (10.0%)	0.69

NICU: Neonatal intensive care unit.

Table 5. Distribution of direct coombs test results.

Direct Coombs result	Exposed n (%)	Unexposed n (%)
Negative	31 (75.6)	10 (24.4)
Positive (0.5–1+)	4 (80.0)	1 (20.0)
Positive (1–2+)	1 (12.5)	7 (87.5)
Positive (≥2+)	3 (100.0)	0 (0.0)

Direct Coombs testing was performed based on clinical indication (n = 57).

DISCUSSION

In our single-center cohort of 196 neonates, infants exposed in utero to maternal SARS-CoV-2 infection exhibited higher rates of hyperbilirubinemia, earlier onset of jaundice, increased NICU admissions, and distinct patterns of direct Coombs test positivity compared with unexposed controls. Notably, these associations were observed despite maternal PCR negativity at delivery and in the absence of increased severe respiratory morbidity or mortality. Together, these findings suggest that resolved maternal COVID-19 may not confer substantial risk for major neonatal complications but may be associated with subtler metabolic and immunologic alterations that are not captured by conventional neonatal outcome measures (12,16). Our results extend prior population-based studies, including large nationwide cohorts, which have reported modest increases in NICU admission and neonatal jaundice following maternal SARS-CoV-2 infection, while consistently demonstrating low rates of severe neonatal disease (12).

Birth anthropometry, Apgar scores, early feeding milestones, postnatal weight trajectories, and respiratory support requirements did not differ between groups. These findings align with large systematic reviews and population-based studies showing that major neonatal outcomes are generally preserved following resolved maternal SARS-CoV-2 infection, even as more subtle metabolic or immunologic alterations may be detectable (7,17-20).

Although NICU admission was more frequent among exposed infants, indications for admission were similarly distributed between groups, and no differences were observed in indicators of disease severity, including length of stay, intensity of respiratory support, and inflammatory markers. This suggests that increased admissions were not accompanied by greater severity of illness. Throughout the study, NICU admission was based on standard clinical indications; no formal category of observation-only admission solely attributable to maternal COVID-19 exposure was established at our institution. Of note, no formal changes in institutional NICU admission criteria occurred during the study period (12,21-23).

A key finding of this study was the higher incidence and earlier onset of hyperbilirubinemia among exposed neonates. Although peak bilirubin levels did not differ significantly between groups, exposed infants developed jaundice earlier and were more likely to require treatment (Table 2). These findings are consistent with reports from multicenter cohorts and case series describing increased rates of neonatal jaundice following maternal SARS-CoV-2 infection during pregnancy and point toward subtle alterations in bilirubin handling rather than overt hepatic dysfunction (24,25).

Table 6. Trimester-specific neonatal respiratory outcomes among exposed infants.

Outcome	1st trimester (n = 22)	2nd trimester (n = 45)	3rd trimester (n = 45)	p-value
Endotracheal intubation (%)	0 (0.0%)	4 (10.0%)	0 (0.0%)	0.034
Intubation duration (days, mean ± SD)	0	1.97 ± 9.51	0	0.036
CPAP requirement (%)	1 (4.8%)	3 (7.5%)	0 (0.0%)	0.41
Combined respiratory support (%)	3 (14.3%)	6 (14.0%)	1 (2.2%)	0.18

SD: Standard deviation, CPAP: Continuous positive airway pressure.

Several mechanisms may account for these observations. Maternal SARS-CoV-2 infection may induce systemic inflammation and cytokine release that alter placental function and disrupt fetal immune programming (16). Altered transplacental transfer of maternal antibodies may subsequently contribute to immune-mediated hemolytic processes in the neonate, while even subtle respiratory adaptation challenges can augment bilirubin production through increased erythrocyte turnover (24,26). Together, these interacting pathways provide a biologically plausible explanation for the earlier onset and higher frequency of hyperbilirubinemia observed in exposed infants, as well as for the distinct patterns of Coombs test severity described below (16,24,26).

Within this context, the pattern of severity on the direct Coombs test provides additional insight. While overall Coombs positivity rates were comparable between groups, high-grade positivity occurred exclusively among exposed infants, whereas weaker positivity predominated among unexposed controls. Direct Coombs testing was performed in a clinically selected subset of infants rather than systematically across the cohort, thereby introducing selection bias. In addition, the relatively small sample size of this subgroup limits statistical power and reduces the generalizability of these findings. Therefore, the observed differences in Coombs test severity should be interpreted with caution (24).

When the timing of maternal infection is considered, our findings provide nuanced insights. In trimester-specific analyses, infants exposed during the second trimester demonstrated a higher frequency of endotracheal intubation than those exposed during the the first or third trimesters, and second-trimester exposure was associated with an increased RR of intubation when first- and third-trimester exposures were combined as the reference. Notably, this association was confined to intubation and was not accompanied by consistent trimester-related differences in other admission-related respiratory outcomes, including CPAP use or combined respiratory support during hospitalization. Given the low absolute number of events and the absence of concordant differences across related endpoints, this finding should be interpreted cautiously and regarded as hypothesis-generating rather than confirmatory. In addition, several RR estimates exceeded 1.0 with wide CIs, reflecting limited event counts and statistical precision.

Placed within the context of existing population-based and longitudinal evidence, these observations are broadly consistent with data suggesting that neonatal morbidity following maternal SARS-CoV-2 infection is generally modest and that adverse neonatal outcomes often occur in the absence of direct neonatal infection (12,27-29). In a Swedish nationwide cohort, maternal SARS-CoV-2 infection during pregnancy was associated with modest increases in neonatal care admission, respiratory morbidity, and hyperbilirubinemia, while neonatal test positivity remained rare; notably, the median interval from maternal test positivity to delivery was 36 days (12). In that study, preterm birth emerged as an important mediator of neonatal respiratory morbidity (12). Similarly, in our cohort, the absence of trimester-related differences across most respiratory endpoints and the low overall frequency of severe respiratory outcomes support the conclusion that serious neonatal respiratory disease is uncommon among exposed but uninfected infants. At the same time, the isolated, trimester-specific intubation signal observed in our data suggests that vulnerability may not be uniform across gestation and raises the possibility that a narrow window of exposure could be associated with more severe respiratory adaptation in a small subset of infants.

Evidence from longitudinal cohorts further clarifies why trimester-dependent effects are not consistently detected when broader respiratory distress endpoints are examined (29). In the COVID Outcomes in Mother Infant Pairs study, respiratory distress among exposed but uninfected neonates was defined by typical clinical signs and radiographic findings (29). However, comparisons across earlier and later gestational exposure did not demonstrate clear trimester-dependent differences in respiratory distress at birth (29). This apparent discrepancy likely reflects differences in outcome definitions and cohort characteristics across studies. Endotracheal intubation represents a more specific marker of severe respiratory compromise than composite respiratory distress measures, and may therefore be more sensitive in identifying clinically meaningful impairments in early respiratory adaptation that are not captured by milder forms of respiratory support, such as CPAP.

Trimester-dependent susceptibility is biologically plausible. Placental development, fetal lung maturation, and immune-inflammatory signaling pathways vary across gestation, and mid-gestation has been proposed as a potentially sensitive window for indirect fetal effects of maternal systemic inflammation (30,31). Variations in placental expression of viral entry-related proteins, such as ACE2 and TMPRSS2, across gestation further support this concept (31,32). However, given the sparse event counts and lack of corroborating trimester differences across other outcomes in our cohort, definitive conclusions cannot be drawn. Larger prospective studies that incorporate standardized neonatal respiratory phenotyping, placental pathology, and inflammatory profiling will be required to determine whether this signal represents a reproducible gestational window of susceptibility.

Within the broader framework of gestational timing, first-trimester exposure warrants brief consideration (9,33). While several reports suggest that asymptomatic or mild infection in early pregnancy is not associated with major adverse neonatal outcomes, systematic reviews have reported increased risks of adverse pregnancy outcomes in the setting of more severe maternal disease (9,34,35). In our cohort, maternal infection that had resolved before delivery was not associated with an increased risk of preterm birth or growth restriction. Several cohorts have found no increase in preterm birth, NICU admission, or growth restriction when maternal infection resolved before delivery (35-37). Taken together, these findings suggest that early pregnancy exposure, when mild or resolved, may spare major neonatal outcomes, while subtle effects related to timing cannot be excluded (36).

Reassuringly, early postnatal follow-up during the first month of life did not reveal differences between exposed and unexposed infants in feeding tolerance, growth, rehospitalization, or screening outcomes, which further indicates that short-term post-discharge health is generally preserved after resolution of maternal infection.

These findings support a risk-stratified approach to postnatal surveillance in which infants exposed to maternal SARS-CoV-2 infection during pregnancy do not require routine escalation of care

based solely on exposure history. However, awareness of potential early bilirubin elevation or challenges in respiratory adaptation may inform individualized monitoring strategies.

Study Limitations

Several limitations should be acknowledged. The retrospective single-center design limits causal inference and generalizability; residual confounding cannot be excluded. Most maternal infections were mild or clinically resolved before delivery, which may limit the generalizability of these findings to severe maternal SARS-CoV-2 infection. Some laboratory and clinical parameters were available only for small subsets of infants and were therefore analyzed descriptively. In addition, all pregnancies in this cohort occurred prior to the availability of COVID-19 vaccination, and our findings may not apply to vaccinated populations or to infections caused by later viral variants.

CONCLUSION

Overall, major neonatal outcomes were largely unaffected by resolved maternal COVID-19; however, our findings suggest subtle, possibly trimester-related differences in neonatal adaptation following in utero exposure. The increased risk of endotracheal intubation among infants exposed during the second trimester suggests a possible window of heightened susceptibility related to respiratory adaptation, while concurrent abnormalities in bilirubin metabolism and patterns consistent with immune-mediated hemolysis may reflect additional physiological processes not captured by conventional neonatal morbidity measures. Despite higher NICU admission rates, no parallel increase in major clinical morbidities or supportive care requirements was observed. Together, these observations support the value of trimester-aware clinical surveillance and underscore the need for prospective studies to clarify underlying mechanisms and optimize neonatal care strategies for exposed infants.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Clinical Research Ethics Committee (approval number 497, dated 31.05.2021).

Informed Consent: The requirement for informed consent was waived because of the study's retrospective nature.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., G.K., M.T., M.B., N.H., İ.M.H., E.Ö., C.T., E.E., E.Ko., Concept: E.K., İ.M.H., E.Ö., C.T., E.E., E.Ko. Design: E.K., G.K., M.T., N.H., İ.M.H., E.Ö., C.T., E.E., E.Ko., Data Collection or Processing: E.K., G.K., M.T., M.B., N.H., A.K., İ.M.H., E.Ö., C.T., E.E., E.Ko., Analysis or Interpretation: E.K., M.T., N.H., A.K., İ.M.H., E.Ö., C.T., E.E., E.Ko., Literature Search: E.K., G.K., M.B., N.H., A.K., İ.M.H., E.Ö., C.T., E.E., E.Ko., Writing: E.K., G.K., M.T., M.B., N.H., A.K., İ.M.H., E.Ö., C.T., E.E., E.Ko.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Supplementary Table 1 Link: https://d2v96fxpocvxx.cloudfront.net/13b035c5-551c-4fd4-a824-19a1febb0519/content-images/3601da28-83e0-45b2-9171-2c364629244a.pdf

REFERENCES

1. Boettcher LB, Metz TD. Maternal and neonatal outcomes following SARS-CoV-2 infection. Semin Fetal Neonatal Med. 2023; 28: 101428.
2. Baud D, Pomar L, editors. Emerging virus infections in adverse pregnancy outcomes. Basel: MDPI; 2022.
3. Shabil M, Gaidhane S, Ballal S, Kumar S, Bhat M, Sharma S, et al. Maternal COVID-19 infection and risk of respiratory distress syndrome among newborns: a systematic review and meta-analysis. BMC Infect Dis. 2024; 24: 1318.
4. Flannery DD, Zevallos Barboza A, Pfeifer MR, Hudak ML, Barnette K, Getzlaff TR, et al. Perinatal COVID-19 maternal and neonatal outcomes at two academic birth hospitals. J Perinatol. 2022; 42: 1338-45.
5. Charuta A, Smuniewska M, Woźniak Z, Paziewska A. Effect of COVID-19 on pregnancy and neonate's vital parameters: a systematic review. J Pregnancy. 2023; 2023: 3015072.
6. Vizheh M, Allahdadian M, Ghasemi-Tehrani H, Muhidin S, Hashemi M, Dehghan M. Maternal and neonatal outcomes of COVID-19 infection in pregnancy. Arch Iran Med. 2023; 26: 43-9.
7. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ. 2021; 193: E540-8.
8. World Health Organization. WHO COVID-19 dashboard. Available from: https://data.who.int/dashboards/covid19/cases. Accessed January 19, 2026.
9. Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020; 25: 100446.
10. Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020; 20: 559-64.
11. Smith V, Seo D, Warty R, Payne O, Salih M, Chin KL, et al. Maternal and neonatal outcomes associated with COVID-19 infection: a systematic review. PLoS One. 2020; 15: e0234187.
12. Norman M, Navér L, Söderling J, Ahlberg M, Hervius Askling H, Aronsson B, et al. Association of maternal SARS-CoV-2 infection in pregnancy with neonatal outcomes. JAMA. 2021; 325: 2076-86.
13. Altman DG. Practical statistics for medical research. London: Chapman and Hall/CRC; 1990.
14. Conover WJ. Practical nonparametric statistics. New York: John Wiley & Sons; 1999.
15. Lydersen S, Pradhan V, Senchaudhuri P, Laake P. Choice of test for association in small sample unordered r x c tables. Stat Med. 2007; 26: 4328-43.
16. Gee S, Chandiramani M, Seow J, Pollock E, Modestini C, Das A, et al. The legacy of maternal SARS-CoV-2 infection on the immunology of the neonate. Nat Immunol. 2021; 22: 1490-502.
17. Zhang D, Huang T, Chen Z, Zhang L, Gao Q, Liu G, et al. Systematic review and meta-analysis of neonatal outcomes of COVID-19 vaccination in pregnancy. Pediatr Res. 2023; 94: 34-42.
18. Murphy CA, O'Reilly DP, Edebiri O, Donnelly JC, McCallion N, Drew RJ, et al. The effect of COVID-19 infection during pregnancy; evaluating neonatal outcomes and the impact of the B.1.1.7 variant. Pediatr Infect Dis J. 2021; 40: e475-81.

19. Pashaei Z, SeyedAlinaghi S, Qaderi K, Barzegary A, Karimi A, Mirghaderi SP, et al. Prenatal and neonatal complications of COVID-19: a systematic review. Health Sci Rep. 2022; 5: e510.
20. Mullins E, Perry A, Banerjee J, Townson J, Grozeva D, Milton R, et al. Pregnancy and neonatal outcomes of COVID-19: the PAN-COVID study. Eur J Obstet Gynecol Reprod Biol. 2022; 276: 161-7.
21. Sankaran D, Nakra N, Cheema R, Blumberg D, Lakshminrusimha S. Perinatal SARS-CoV-2 infection and neonatal COVID-19: a 2021 update. NeoReviews. 2021; 22: e284-95.
22. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy - SET-NET, 16 jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 1635-40.
23. Anderson NB, Calkins KL. Neonatal indirect hyperbilirubinemia. NeoReviews. 2020; 21: e749-60.
24. Al-Matary A, Almatari F, Al-Matary M, AlDhaefi A, Alqahtani MHS, Alhulaimi EA, et al. Clinical outcomes of maternal and neonate with COVID-19 infection - multicenter study in Saudi Arabia. J Infect Public Health. 2021; 14: 702-8.
25. Itriago E, Lingappan K, Teruya J, Dinu D. Hemolysis in neonates born to mothers with history of SARS-CoV-2 infection during pregnancy: a case series. Int J Clin Pediatr. 2022; 11: 27-32.
26. Itriago E, Lingappan K, Teruya J, Dinu D. Hemolysis in neonates born to mothers with history of SARS-CoV-2 infection during pregnancy: a case series. Int J Clin Pediatr. 2022; 11: 27-32.
27. Schell RC, Macias DA, Garner WH, White AM, McIntire DD, Pruszynski J, et al. Examining the impact of trimester of diagnosis on COVID-19 disease progression in pregnancy. Am J Obstet Gynecol MFM. 2022; 4: 100728.
28. Song D, Prahl M, Gaw SL, Narasimhan SR, Rai DS, Huang A, et al. Passive and active immunity in infants born to mothers with SARS-CoV-2 infection during pregnancy: prospective cohort study. BMJ Open. 2021; 11: e053036.
29. Man OM, Azamor T, Cambou MC, Fuller TL, Kerin T, Paiola SG, et al. Respiratory distress in SARS-CoV-2 exposed uninfected neonates followed in the COVID Outcomes in Mother-Infant Pairs (COMP) Study. Nat Commun. 2024; 15: 399.
30. Argueta LB, Lacko LA, Bram Y, Tada T, Carrau L, Rendeiro AF, et al. Inflammatory responses in the placenta upon SARS-CoV-2 infection late in pregnancy. iScience. 2022; 25: 104223.
31. Chen J, Neil JA, Tan JP, Rudraraju R, Mohenska M, Sun YBY, et al. A placental model of SARS-CoV-2 infection reveals ACE2-dependent susceptibility and differentiation impairment in syncytiotrophoblasts. Nat Cell Biol. 2023; 25: 1223-34.
32. Indra S, Chalak K, Das P, Mukhopadhyay A. Placenta a potential gateway of prenatal SARS-CoV-2 infection: a review. Eur J Obstet Gynecol Reprod Biol. 2024; 303: 123-31.
33. Piekos SN, Roper RT, Hwang YM, Sorensen T, Price ND, Hood L, et al. The effect of maternal SARS-CoV-2 infection timing on birth outcomes: a retrospective multicentre cohort study. Lancet Digit Health. 2022; 4: e95-104.
34. Marchand G, Patil AS, Masoud AT, Ware K, King A, Ruther S, et al. Systematic review and meta-analysis of COVID-19 maternal and neonatal clinical features and pregnancy outcomes up to June 3, 2021. AJOG Glob Rep. 2022; 2: 100049.
35. Rodriguez-Wallberg KA, Nilsson HP, Røthe EB, Zhao A, Shah PS, Acharya G. Outcomes of SARS-CoV-2 infection in early pregnancy: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2024; 103: 786-98.
36. Tang Y, Chen L, Han T, Hu C, Li P, Tang J, et al. The impact of acute and prior SARS-CoV-2 infection on maternal and neonatal outcomes in pregnant women: a single-center retrospective cohort study. BMC Pregnancy Childbirth. 2025; 25: 181.
37. Cosma S, Carosso AR, Cusato J, Borella F, Bertero L, Bovetti M, et al. Obstetric and neonatal outcomes after SARS-CoV-2 infection in the first trimester of pregnancy: a prospective comparative study. J Obstet Gynaecol Res. 2022; 48: 393-401.