



## Covid-19 Pandemisi Sırasında Üçüncü Basamak Referans Bir Yenidoğan Yoğun Bakım Ünitesinde Çok Preterm Doğum Oranları

### Very Preterm Birth Rates at a Referral Tertiary Neonatal Intensive Care Unit During Covid-19 Pandemic

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#### ABSTRACT

**AIM:** IT is known that one of the important effects of viral diseases on pregnancy and fetus is preterm delivery. We aim to evaluate the impact of the COVID-19 pandemic on the frequency of very preterm (<32 weeks gestational age) infant admission at a referral tertiary neonatal intensive care unit in Turkey.

**MATERIAL AND METHOD:** Very preterm infant admission rates to Neonatal Intensive Care Unit from September 2019-February 2020 before the pandemic and the same period of the year after the pandemic (September 2020-February 2021) were retrospectively compared. Maternal/ neonatal characteristics and perinatal risk factors were collected from patient records.

**RESULTS:** A total of 1687 infants were admitted to the NICU during the 6 months before the pandemic, 266 (15.7%) of them were very preterm infants. The number of total admissions was 1648 and 230 (13.9%) of them were very preterm during the pandemic. About a 2% decrease in admission rates was not statistically significant. Mean gestational age ( $28 \pm 2.7$  and  $29 \pm 2.8$  weeks), mean birth weight ( $1370 \pm 531$  and  $1327 \pm 517$  g), and other basic maternal and neonatal characteristics were similar ( $p > 0.01$ ).

**CONCLUSION:** Pandemic and its restrictions may have affected to outcomes of pregnancy by indirect mechanisms such as changes in daily activities, social and economic effects, benefiting of health services. Although the number of preterm admission between the two periods seems to have no difference considering a limited cohort and short-term evaluation, these results should be supported by national data.

**Keywords:** COVID-19, preterm births, pandemic, pregnancy

#### ÖZET

**AMAÇ:** Viral hastalıkların gebelik ve fetus üzerindeki önemli etkilerinden birinin preterm doğum olduğu bilinmektedir. Bu çalışmada, COVID-19 pandemisinin Türkiye’de bir üçüncü basamak yenidoğan yoğun bakım ünitesine kabul edilen çok erken preterm (<32 gebelik haftası) bebeklerin sıklığı üzerindeki etkisinin değerlendirilmesi amaçlanmıştır.

**GEREÇ VE YÖNTEM:** Yenidoğan Yoğun Bakım Ünitesine (YYBÜ) pandemi öncesi Eylül 2019-Şubat 2020 ve pandemi sonrası yılın aynı dönemi (Eylül 2020-Şubat 2021) çok preterm (<32 hafta) bebek yatış oranı retrospektif olarak karşılaştırıldı. Maternal/ neonatal özellikler ve perinatal risk faktörleri hasta kayıtlarından elde edildi.

**BULGULAR:** Pandemi öncesi 6 aylık dönemde yenidoğan yoğun bakım ünitesine toplam 1687 bebek yatışı olduğu ve 266’sının (%15.7) <32 hafta preterm olduğu görüldü. Pandemi sonrası dönemde ise toplam yatış sayısı 1648, preterm yatış sayısı 230 (%13.9) idi. Yatış sıklığında yaklaşık %2’lik düşüşün istatistiksel olarak anlamlı olmadığı görüldü. Her iki dönemde gestasyon haftası ( $28 \pm 2.7$  ve  $29 \pm 2.8$  hafta), doğum ağırlığı ( $1370 \pm 531$  ve  $1327 \pm 517$  g), ve diğer temel maternal ve neonatal özellikler benzerdi ( $p > 0.01$ ).

**SONUÇ:** Pandemi ve beraberindeki kısıtlamalar; günlük yaşam alışkanlıkları, sosyal ve ekonomik etkiler, sağlık hizmetlerinden faydalanma gibi dolaylı mekanizmalarla gebelik sonuçlarını etkilemiş olabilir. İki dönem arasında preterm kabul sayısında anlamlı bir fark gözlemlenmemekle birlikte, çalışmanın sınırlı bir kohort ve kısa dönemli bir değerlendirme içermesi göz önünde bulundurularak, elde edilen sonuçların ulusal verilerle desteklenmesi gerektiği düşünülmektedir.

**Anahtar kelimeler:** COVID-19, preterm doğum, pandemi, gebelik

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## INTRODUCTION

Prematurity is a complex and challenging pathophysiological condition. Preterm birth rates are approximately 10% globally. In some European countries, prematurity rates are 4%-5% and in some parts of Africa and Asia, the rates reach 15%-18%. The etiology of preterm birth depends on reasons such as socio-demographic, medical, obstetric, fetal, psychosocial, and environmental factors (1,2). It has been known that viral infections during pregnancy may lead to fetal loss, perinatal adverse outcomes, and prematurity. Most descriptive studies from previous influenza pandemics have reported higher rates of preterm birth among infected pregnant women however systematic reviews found inconsistent findings from comparative epidemiological studies (3-5). In December, 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China (6). COVID-19 was declared a pandemic in March 2020 by the World Health Organization (WHO). The SARS-CoV-2 causes a multi-organ infection and most often manifests clinically as fever, cough, dyspnea, and myalgia. Previous several case studies suggest a preterm delivery rate as high as 47% (7-9). Sahin D. et al.; reported that the most common pregnancy complication was preterm labor (2.9%) followed by miscarriage (2.1%) among SARS-CoV-2 infected pregnant women in a large perinatology unit in Turkey (10). An exaggerated inflammatory response, maternal hypoxia, dysregulated cytokine production, and COVID-19-related coagulopathy have all been proposed as potential pathophysiological mechanisms contributing to adverse obstetric outcomes in affected pregnancies.

By declaration of pandemics by WHO and subsequently with the Turkish Ministry of Health; a bunch of regulations were made to prevent the spread of the virus such as curfew, the closing of all schools and workplaces, etc. as well as the changes made in health care centers' daily practice for instance postponement of non-emergency patients and planned interventions, shifting healthcare professionals into the care of COVID 19 patients, etc. Turkish Ministry of Health has pursued an effective and rational policy since the beginning of the pandemic. The pandemic process was successfully managed in line with the recommendations of the established scientific committee and the spread of the disease was brought under control in a short period of time (11). Pandemic and its restrictions have had implications, including changes in daily activities, social and economic effects, and access to health care, which may alter preterm birth risk. Although according to recent studies the number of preterm admissions seems to have decreased, studies reporting an increase in the rates of preterm birth and stillbirth have also been published (12-18). High-quality evidence on COVID-19 associated risk of adverse perinatal outcomes is essential, for clarifying expectations for improved pregnancy outcomes and expanding COVID-19 immunization. Given the inconsistent evidence and public health importance of this topic, we designed to study the impact of the COVID-19 pandemic on the frequency of very preterm infant admissions and its effects on morbidities and mortality at a referral tertiary neonatal intensive care unit in Turkey.

## MATERIAL AND METHOD

This study was held in an extensive referral center for middle, east, and north Turkey for high-risk pregnancies. The hospital started to serve for the first time on 01 September 2019; as a referral unit for perinatal-neonatal medicine with 150 bed level III neonatal intensive care unit (NICU) and 93 bed perinatology units. Before the COVID-19 pandemic was affirmed, the hospital was serving only for 6 months during September 2019-February 2020 (Period 1). The aforementioned restrictions were valid during the first wave and gradually lessened by June 2020 in Turkey. To study the effect of the first wave of the pandemic and the related restrictions' the same period of the year following the first wave of the pandemic September 2020-February 2021 (Period 2) was evaluated. Comparison was made including the same months of the following years to avoid the seasonal effect on preterm births and admission rates.

Preterm newborns are defined as infants born alive before the completion of 37 weeks of gestation. Very preterm infant which is defined as gestational age less than 32 weeks admission rates

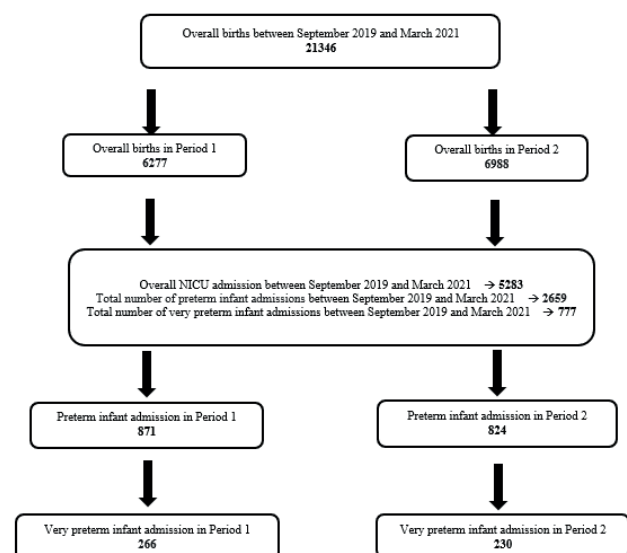
to the NICU was retrospectively compared between Period 1 and 2. Maternal and neonatal characteristics, perinatal risk factors, preterm morbidities, and rates were collected from patient records. Maternal characteristics, including age, presence of maternal infections, mode of delivery, and the rates of preeclampsia, eclampsia, gestational hypertension, and gestational diabetes, were recorded. Neonatal characteristics, such as birth weight, gestational age, gender, and the 1st and 5th minute APGAR scores, were also included in the analysis. The rates of preterm morbidities—including respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and early- and late-onset sepsis—was compared between two periods. RDS was defined by clinical signs of respiratory distress along with the need for surfactant therapy (19). Among infants diagnosed with PDA, only those with hemodynamically significant PDA were included (20). NEC was defined as stage II or higher according to the modified Bell's staging criteria (21). For BPD, only cases classified as moderate to severe were considered (22). IVH was diagnosed based on cranial ultrasonography findings and graded according to the Papile classification system (23). Sepsis was defined by clinical and laboratory indicators suggestive of infection or by positive blood cultures. Early-onset sepsis (EOS) was defined as occurring within the first 72 hours of life, while late-onset sepsis (LOS) was defined as sepsis occurring thereafter (24). Detection of SARS-CoV2 in nasopharyngeal and oropharyngeal samples was performed by Real Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method targeting RdRp (RNA dependent RNA polymerase) gene.

Baseline characteristics were compared using Student's t-test and chi-squared test or Fisher's exact tests where appropriate. All analyses were performed using SPSS, version 22. The study was approved by the local Clinical Research Ethics Committee (E2-21-169) at Ankara Bilkent City Hospital.

## RESULTS

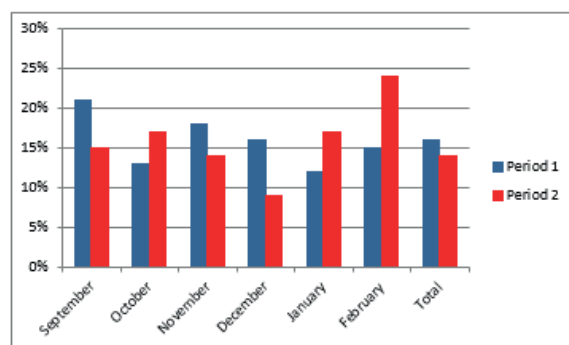
The number of total births at the hospital between September 2019 and March 2021 was 21346; 6277 of them occurred in Period 1. The number of total admissions to the NICU was 5283 (24%) and 891 (%16) of them were very preterm infants. The number of inborn very preterm infants born September 2019 and March 2021 was 777. A total of 1687 infants were admitted to the NICU during Period 1, 871 (52%) of them were preterm, and 266 (15.7%) of them were very preterm infants. The number of total admissions was 1648, the number of preterm was 824 (50%) and 230 (13.9%) of them were very preterm in Period 2, this slight decrease in admission rates was not statistically significant.

Figure 1. Flow diagram



Very preterm infant admission rates month by month in both periods were represented in

**Figure 2.** Comparison of very preterm birth rates between two periods



Period 1: September 2019-February 2020, Period 2: September 2020-February 2021

A significant decrease in the admission rate was observed in December 2020 when compared with December 2019 (9 % vs. 16 %,  $p=0.02$ ). However, the admission rates were comparable in other months (Figure 2). When we compared very preterm infant admission rates from September 2019-March 2020 before the pandemic was declared and the following 7-months of the pandemic (April 2020-October 2020) we observed a significant decrease in the admission rates (15.7% vs. 12.7 %,  $p=0.04$ ). The number of total admissions was 2094 and 266 (12.7%) of them were very preterm during the pandemics. About a 4% decrease in admission rates was statistically significant ( $p=0.04$ ). The number of infants born from mothers with evidence of COVID-19 was 25 (5.3 %) in Period 2. The basic maternal and neonatal characteristics were represented in Table 1 and no statistically significant difference was observed in any of the features assessed.

**Table I.** Basic maternal and neonatal characteristics of the groups

	Period 1	Period 2	p
<b>Total numbers of very preterm infants</b>	266	230	
<b>Ethnicity/Race</b>			
Turkish citizen	254 (95%)	216 (93%)	1.000
<b>Neonatal characteristics</b>			
Birth weight, g $\pm$ SD	1370 ( $\pm$ 531)	1327 ( $\pm$ 517)	0.859
Gestational age, weeks $\pm$ SD	28 ( $\pm$ 2.7)	29 ( $\pm$ 2.8)	0.283
Male gender, n (%)	169 (59.3)	122 (53.3)	0.116
APGAR 1.min $\pm$ SD	5 ( $\pm$ 1.6)	5 ( $\pm$ 1.8)	0.082
APGAR 5.min $\pm$ SD	7 ( $\pm$ 1.6)	6 ( $\pm$ 1.8)	0.047
<b>Maternal characteristics</b>			
Maternal age $\pm$ SD	28 ( $\pm$ 5.3)	29 ( $\pm$ 6)	0.410
Cesarean section, n (%)	259 (90.9)	210 (91.3)	0.896
Fetal distress, n (%)	75 (28)	72 (30)	0.735
Preeclampsia, n (%)	25 (8.8)	61 (26.4)	0.125
Eclampsia, n (%)	2 (0.7)	5 (1)	1.000
Gestational hypertension, n (%)	8 (2.8)	19 (8.3)	0.544
Gestational diabetes, n (%)	8 (2.8)	27 (11.7)	0.105
Maternal infections, n (%)	11 (3.9)	20 (8.7)	1.000

SD: Standard Deviation

Very preterm infant mortality rates (26.5% vs. 26.1%) were comparable between the two periods ( $p>0.86$ ). The number of stillbirth was 86 (1.4%) in Period 1 and 109 (1.5%) in Period 2 ( $p=0.76$ ). Antenatal steroid administration rates were similar between the two periods (13.3% vs. 13.1,  $p=0.85$ ).

During the study period, 1416 pregnant women tested positive for COVID-19 by PCR. Preterm delivery was observed in 160 of these cases (11.3%). Number of infants born to COVID-19 positive mothers was 1432 and 177 of these were admitted to NICU.

The comparison of the incidence of neonatal morbidities among all preterm infants across the two periods is presented in Table 2. The incidence of common neonatal morbidities was comparable between groups except the higher RDS rate observed in Period 2

**Table II.** Comparison of neonatal morbidities between the two periods

Morbidities	Pre-COVID (n=281)	Post-COVID (n=496)	p
Respiratory Distress Syndrome, n(%)	208 (74)	441 (89)	<0.001*
Patent Ductus Arteriosus, n(%)	91 (32)	136 (27)	0.284
Intraventricular Hemorrhage, n(%)	60 (21)	81 (16)	0.1
Bronchopulmonary Dysplasia, n(%)	56 (20)	93 (19)	0.706
Retinopathy of Prematurity, n(%)	38 (13)	69 (14)	0.738
Early Neonatal Sepsis, n(%)	71 (25)	88 (18)	0.016
Late Neonatal Sepsis, n(%)	162 (57)	272 (55)	0.319
Necrotizing Enterocolitis, n(%)	36 (13)	51 (10)	0.344
Duration of hospitalization; days Mean $\pm$ SD	37 ( $\pm$ 33)	39 ( $\pm$ 37)	0.520

Pre-COVID: Period between September 2019-February 2020, Post-COVID: Period between February 2020-February 2021, SD: Standard Deviation

## DISCUSSION

Our results suggest that the first wave of the COVID-19 pandemic has no effect on very preterm infant admission rates in a busy referral tertiary NICU. Monthly comparisons of very preterm birth rates before and during the pandemic revealed a variable pattern. A decrease was observed in September, November, and December, which may reflect reduced exposure to infections and environmental stressors due to public health measures. In contrast, an increase was noted in October, January, and especially February, potentially related to delayed effects of the pandemic on maternal health, such as reduced access to antenatal care or increased psychosocial stress. These fluctuations suggest that the impact of the pandemic on very preterm birth rates is likely multifactorial and influenced by both healthcare system changes and broader societal factors. Mostly restrictions to travel between cities and postponed planned doctor visits just during the first wave lead to a reduction in admission rates however these admission rates become comparable with lessening the restrictions suggesting that, the reduction during the pandemic is probably caused by the regulations made to prevent to virus spread; not the disease itself. Basic maternal/neonatal characteristics and the cause of prematurity were also not significantly different between the two periods according to our results.

Numerous investigators studied the effect of the COVID-19 pandemic on preterm births; however, the findings of these studies were inconsistent. Similar to our results a nationwide study from Sweden did not find any associations between being born during restrictions of COVID-19 were enforced and the risk for any of the preterm birth categories or stillbirth (25). Although the result was similar, as opposed to the single-center study of us, the Swedish study was nationwide. Furthermore; Main et al. found no reduction in preterm birth rates in their study which they assessed the impact of the pandemic on preterm birth rates (<37 weeks) during the peak months of the pandemic (26). Despite the overall rate of preterm birth being unchanged there observed an increase of 28 to 31 %, week, unlike our results. Recently, two hospitals in Philadelphia did not detect significant changes in preterm or stillbirth rates during the pandemic period (March-June 2020) with the same months in 2018 and 2019 (27). This result was from data from preterm infants born before 37 weeks and the study had a smaller sample size than our study. According to the single-center study in England, the incidence of stillbirth was significantly higher during the pandemic period and there were no significant differences in the rates of preterm births (16). Unlike our study, they used data of preterm birth under 37 weeks' gestation however they had smaller sample sizes. The results of the study from Italy, which



was violently affected by the pandemic, showed a statistically significant increase in stillbirths and an insignificant increase in very preterm birth rates (17). Unlike the previously mentioned studies, authors from Denmark, Ireland, Philadelphia, France, United States and Canada reported a significant decrease in preterm births as well as a reduction in live births of very low birth weight infants (12-14,28-30). Simon et al. observed higher gestational hypertension and clinical chorioamnionitis rates despite the lower very preterm and very-low-birth-weight birth rates (28). Unfortunately, our results did not support any changes in maternal prematurity-related morbidities. When the cause of prematurity was investigated a large retrospective cohort study showed that only iatrogenic preterm birth rates decreased and spontaneous preterm birth rates did not change with the pandemics (31). Unlike all previous reports, a study from China showed an increase in the rates of preterm birth (18). We thought that the variable results obtained from different countries all over the world may be related to the measures taken by the countries to prevent the spread of the virus and the strict compliance of the people to them, rather than the frequency of disease in pregnant women and the possibility of fetal impact. However, mortality rates in pregnant women were not reported in previous works as we didn't in our study. There is a possibility that increased deaths in pregnant women in earlier stages of pregnancy did have some effect on the proportion of preterm births.

In our study, the rates of preterm morbidities were similar between two periods except the higher RDS rate observed in Period 2. This similarity may be attributed to factors such as the consistent quality of neonatal care and comparable gestational age distributions, despite healthcare disruptions during the pandemic. Similar studies comparing preterm morbidities between the pandemic and pre-pandemic periods have reported varying results. A single center study from Turkey comparing the first year of the pandemic with the preceding year found no significant differences in the rates of RDS, NEC, and PDA (32). Data of a multicenter study from Italy showed that there is no change in rates of NEC or LOS during first year of the pandemic (33). In contrast, the Swedish study with a large number of cases reported a significant decrease in the incidence of NEC and LOS rates (34).

Being a single-center experience and retrospective design are important limitations of this study. The course of the COVID 19 pandemic has been highly variable in time due to the mutations of the virus, increased virulence and the severity of the disease, and the emergence of different variants. As of this study period, it only covers cases in the post-first wave, alpha variant period. It should be noted that the impact of disease on preterm birth after the emergence of delta variants and omicron variants could be different. Furthermore, some additional factors that may have an impact on preterm births such as the lack of other circulating viruses during the pandemic, detailed pregnancy follow-up data (such as timing and frequency of antenatal visits), and maternal mortality rates were not evaluated.

## CONCLUSION

The inconsistency of results could be attributed to the differences in restriction orders of the pandemic, population heterogeneity, health system, and the number of COVID-19 cases between countries. Recommendations for antenatal care during pandemics include ensuring continued access to routine prenatal visits, early identification of at-risk pregnancies, and the importance of maternal vaccination and infection control practices to reduce COVID-19-associated complications. The exact impact of the COVID-19 on pregnant women and fetal/neonatal health is yet to be clarified and further larger well-designed multicenter investigations are warranted.

## Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: HGKK; data collection: GÇ, NT, EÖT; analysis and interpretation of results: HGKK, GÇ; draft manuscript preparation: GÇ, HGKK, CT, DŞ. All authors reviewed the results and approved the final version of the article for publication.

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