Fetal Diaphragmatic Excursion Is Decreased in Hospitalized Pregnant Women Infected with COVID-19 during the Second and Third Trimesters

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Abstract

Objective In the present study, we aimed to evaluate coronavirus disease 2019 (COVID-19) infection effects on fetal diaphragm thickness and diaphragmatic excursion, which together show the quality of diaphragmatic contractions.

Study Design One hundred and ninety-two pregnant women were included in this prospective case–control study. Patients were divided into four groups according to their COVID-19 infection history in their second or third trimester: hospitalized COVID-19-infected pregnant women group ($n = 48$), outpatient COVID-19-infected pregnant women group ($n = 48$), common cold (COVID-19 polymerase chain reaction negative) pregnant women group ($n = 48$), and noninfected healthy controls ($n = 48$). The number of patients was determined by power analysis following the pilot study. All participants underwent an ultrasound examination to determine fetal diaphragm parameters at 32 to 37 weeks of gestation.

Results Demographic characteristics were similar among the four groups. The gestational age at ultrasound examination and gestational age at delivery were similar among the groups. Neonatal intensive care unit (NICU) admission rate was significantly higher in the hospitalized COVID-19-infected pregnant women group than the other groups. The fetal diaphragm thickness during inspiration and expiration, and fetal costophrenic angles at inspiration and expiration were similar among the groups. Fetal diaphragmatic excursion was significantly decreased in the hospitalized COVID-19-infected pregnant women group compared with the other groups.

Conclusion Our results indicated that moderate maternal COVID-19 infection decreased fetal diaphragmatic excursion, and ultrasonographic evaluation of fetal diaphragmatic excursion before delivery can provide critical information to predict whether infants will require NICU admission.

Keywords

- COVID-19 infection
- fetal diaphragm thickness
- fetal diaphragmatic excursion
- NICU admission

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Key Points

- Diaphragm ultrasound as a new technique for characterizing the diaphragm's structure and function.
- Fetal diaphragmatic excursion is decreased in the presence of moderate COVID-19 infection.
- Ultrasonographic evaluation of fetal diaphragmatic excursion provides critical information to predict NICU admission.

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has procoagulant features that increase hypoxia in infected individuals.[1] The risk of SARS-CoV-2 infection does not increase during pregnancy; however, pregnant women have worse coronavirus disease 2019 (COVID-19) clinical outcomes than similarly aged nonpregnant women.[2] In the literature, it is well documented that COVID-19 is associated with preterm labor, fetal distress, and stillbirth.[2,3] Further, neonates born to COVID-19-infected mothers are more likely to be admitted to neonatal intensive care units (NICUs).[4] This is consistent with the previously described fetal inflammatory response syndrome caused by maternal infection.[5] Similarly, the hypercoagulopathy, increased inflammatory response, and hypoxia caused by COVID-19 might affect fetal pulmonary circulation.

Recently, researchers have explored the potential of a diaphragm ultrasound as a new technique for characterizing the diaphragm's structure and function. Utrasonographic evaluation of diaphragm is a noninvasive method that can provide information for both diaphragm excursion and thickness. The diaphragmatic thickening ratio measures the diaphragm's capacity to contract, which may correlate with its strength.[6] Diaphragm ultrasonography can be used to detect severe diaphragm weakness in critically ill adult patients.[7,8] Moreover, measuring the diaphragm thickness and diaphragm thickness fraction may be useful for assessing the efficiency of diaphragmatic contractions during the respiratory cycle.[9]

COVID-19 might affect fetal pulmonary circulation and pulmonary and diaphragm function because of the induced hypercoagulopathy, hypoxia, and excessive inflammatory response. To the best of our knowledge, the diaphragmatic function in fetuses with COVID-19-infected mothers has not been assessed. Hence, in the current study, we aimed to evaluate the effects of COVID-19 infection on fetal diaphragm thickness and diaphragmatic excursion, which show the quality of diaphragmatic contractions. We hypothesized that fetuses who suffer from COVID-19 infection are at risk of adverse respiratory outcomes, and this risk can be determined by evaluating fetal diaphragm ultrasound measurements.

Materials and Methods

This prospective case–control study was conducted in Kayseri City Hospital Obstetric Clinic in Turkey after obtaining approval from the ethics committee of Kayseri City Hospital (approval no.: 507) in accordance with the Declaration of Helsinki.

Study Population and Exclusion Criteria

One hundred and ninety-two pregnant women were included in this prospective case–control study. Patients were divided into four groups according to their COVID-19 infection history in their second or third trimester: hospitalized COVID-19-infected pregnant women group ($n = 48$), outpatient COVID-19-infected pregnant women group ($n = 48$), common cold (COVID-19 polymerase chain reaction [PCR] negative) pregnant women group ($n = 48$), and noninfected healthy controls ($n = 48$). The number of patients was determined by power analysis following the pilot study. Patients with multifetal pregnancies, fetal structural anomalies, gestational hypertension, preeclampsia, eclampsia, pregestational diabetes mellitus, gestational diabetes mellitus, placenta invasion anomalies, fetal growth restriction, prematurity, preterm premature rupture of membranes, urgent need for cesarean section (fetal distress), and maternal systemic disease were excluded. In addition, we excluded patients receiving betamethasone as treatment for preterm delivery because it is a corticosteroid medication that can affect the diaphragm muscle. Patients whose birth data could not be assessed, who continued their follow-up in a different hospital, or did not agree to participate in the study were excluded (►Fig. 1).

Definitions

A throat swab was used to determine a positive COVID-19 infection, which was assessed using a real-time reverse-transcriptase PCR assay. Delphi consensus criteria were preferred for fetal growth restriction diagnosis.[10] The American Thoracic Society/Infectious Diseases Society of America guidelines were used to divide COVID-19 disease into mild, moderate, or severe illness.[11] Patients who had severe disease were excluded due to poor prognosis and medications that effect fetus diaphragm. The gestational age was calculated according to the last menstrual period. The primary outcome of the study was COVID-19 infection effects on fetal diaphragm thickness and diaphragmatic excursion, which show the quality of diaphragmatic contractions.

Ultrasonographic Evaluation

One experienced clinician (M.E.S.) conducted the ultrasound examinations between 32 and 37 weeks of gestation using a Philips ClearVue 550 ultrasound machine with a 3.5-MHz convex array transducer at the first visit after discharge in hospitalized pregnant women. In other groups, ultrasound examinations were conducted between 32 and 37 weeks of gestation at their routine visits. Ultrasonographic measurements were performed as previously described in the literature.[12]

The diaphragm was measured during inspiration and expiration. The probe was placed on the maternal abdomen perpendicular to the left and right chest walls and below the costal margin to obtain a horizontal view of the fetal diaphragm and diaphragm that has three layers was visualized. The diaphragmatic excursion values were expressed as the

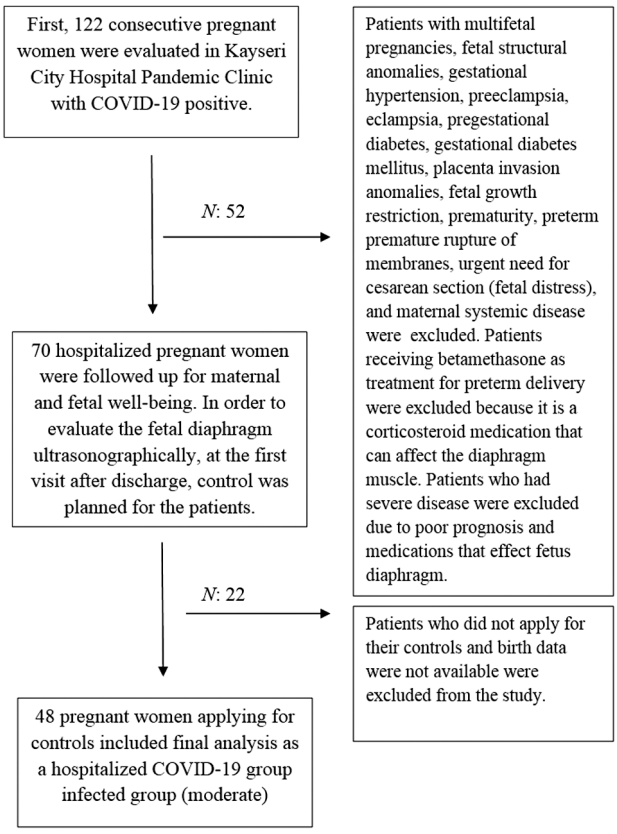

Fig. 1 Flow chart of study population. Note: According to the power analysis, 48 patients per group were necessary. The patient flow chart was continued until reaching 48 hospitalized COVID-19-infected patients who met the criteria. Since the groups were determined at a ratio of 1:1, 48 consecutive pregnant women who met the inclusion and exclusion criteria were included during their routine controls as the control group, 48 pregnant women with common cold (COVID-19 PCR negative), and 48 pregnant women as outpatient COVID-19-infected group (mild). COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

mean value of the left and right sides. M.E.S. did not assess gasping or "picket-fence" breathing during examinations. Since the diaphragm moves up and down during the respiratory cycle, we evaluated two respiratory cycles on the left and right sides of the diaphragm. The average distance between the highest and lowest points of the diaphragm in the fetal chest was calculated. The diaphragmatic excursion is the distance between these two points, which indicates the diaphragm's capacity for movement during the respiratory cycle. We also measured the costophrenic angle during inspiration and expiration using related evaluations (►**Fig. 2**).

Statistical Analysis

In the pilot study leading to this research, the diaphragmatic excursion in the hospitalized COVID-19-infected group ($n = 15$) and the healthy control group ($n = 15$) was analyzed. The diaphragmatic excursion was 4.96 ± 0.72 in the control group and 4.34 ± 0.61 in the hospitalized COVID-19-infected group. According to the power analysis, $\alpha = 0.05$, group ratio 1:1, power $(1 - b) = 0.8$, and effect size calculated as 0.539, 44 patients per group were necessary. When a 10% drop rate was added, 48 patients per group were required, necessitating 192 patients in total.

Statistical analyses were done using Statistical Package for the Social Sciences version 18 (IBM Inc., Armonk, NY). The Kruskal–Wallis' *H*-test was used for determining the normality of the data. The Levene's test was used to evaluate the assumption of variance homogeneity; values are expressed as the mean ± standard deviation, median (minimum–maximum), or *n* (%). A $p < 0.05$ was considered statistically significant. One-way analysis of variance was performed to compare multiple groups (Tukey's post hoc test) and after evaluating for normal distribution. Comparison of categorical data in paired groups was made by chi-square test, while comparison of noncategorical data in paired groups was made by Mann–Whitney's *U*-test.

Results

Comparisons of maternal demographic characteristics and perinatal outcome results are provided in ►**Table 1**. Maternal age ($p = 0.540$), body mass index at ultrasonographic examination ($p = 0.220$), nulliparity ($p = 0.690$), ethnicity ($p = 0.680$), previous cesarean delivery rates ($p = 0.740$), and smoking rates ($p = 0.440$) were similar among the groups. The gestational ages at delivery and birth weight were similar among the groups ($p = 0.820$ and $p = 0.240$). NICU admission rates were significantly increased in the

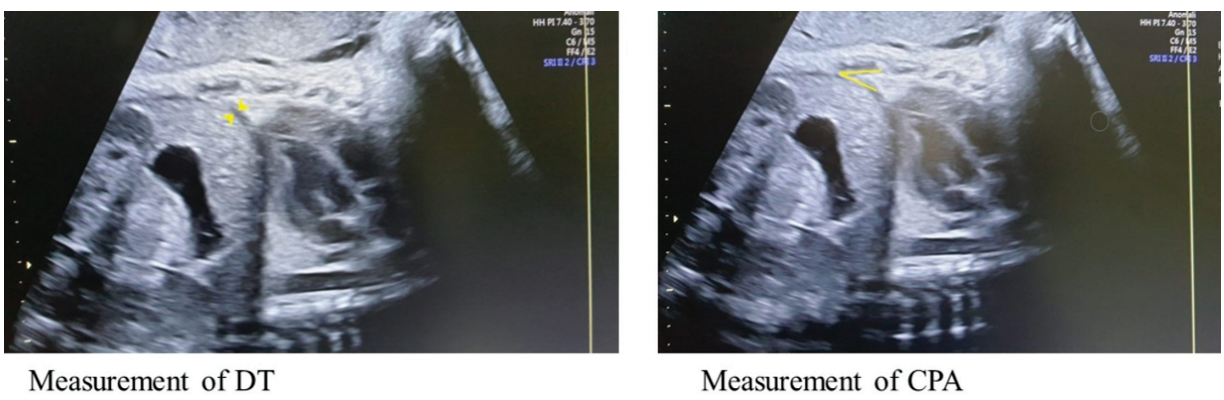

Fig. 2 Ultrasonographic evaluation of fetal diaphragm. CPA, costophrenic angle; DT, diaphragm thickness.

Table 1 Comparison of maternal demographic characteristics and perinatal outcomes among the groups

	Control group ($n = 48$)	Common cold group (COVID-19 PCR negative) ($n = 48$)	Outpatient COVID-19-infected group (mild) ($n = 48$)	Hospitalized COVID-19-infected group (moderate) ($n = 48$)	*p*-Value
Maternal characteristic					
Maternal age (y)	29.6 ± 4.2	28.4 ± 3.8	29.8 ± 4.1	30.2 ± 3.9	0.540
BMI at ultrasound examination (kg/m^2)	29.4 ± 2.7	28.9 ± 2.8	30.1 ± 2.6	30.0 ± 3.1	0.220
Nulliparity	15 (31.25)	14 (29.1)	13 (27)	15 (31.25)	0.690
Ethnicity	46 (95.8)	45 (93.7)	46 (95.8)	45 (93.7)	0.680
Previous CS history	16 (33.3)	17 (35.4)	17 (35.4)	18 (37.5)	0.740
Smoking	6 (12.5)	6 (12.5)	7 (14.5)	5 (10.4)	0.440
Perinatal outcomes					
Gestational age at delivery (wk)	39 (38–40)	39 (38–40)	38 (37–39)	37 (37–39)	0.820
Prematurity (before 37 wk)	2 (4.1)	1 (2.0)	2 (4.1)	3 (6.25)	0.540
Birth weight (g)	3,450 ± 350	3,420 ± 320	3,310 ± 290	3,240 ± 320	0.240
Male gender	27 (56.2)	26 (54.1)	28 (58.3)	24 (50)	0.480
Apgar score at 5 min	9 (8–10)	9 (9–10)	9 (9–10)	9 (8–10)	0.680
NICU admission	1 (2.8)[a]	1 (2.8)[a]	2 (4.1)[a]	6 (12.5)[b]	0.036

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CS, cesarean section; NICU, neonatal intensive care unit; PCR, polymerase chain reaction.
Note: Different superscripts mean statistically significant.

hospitalized COVID-19-infected pregnant women group compared with other groups ($p = 0.036$).

►**Table 2** provides the results of ultrasonographic evaluations. The gestational age at ultrasound examination was similar among the groups ($p = 0.740$). Fetal diaphragm thickness during inspiration and fetal diaphragm thickness during expiration were similar among the groups ($p = 0.450$ and 0.680). Fetal costophrenic angle at inspiration and fetal costophrenic angle at expiration ($p = 0.280$ and $p = 0.390$) were statistically similar among the groups. The fetal diaphragmatic excursion was 4.92 ± 0.70 in the control group, 4.86 ± 0.74 in the common cold (COVID-19 PCR negative) pregnant women group, 4.90 ± 0.68 in the outpatient COVID-19-infected pregnant women group, and 4.34 ± 0.51 in the hospitalized COVID-19-infected pregnant women group. Fetal diaphragmatic excursion was significantly decreased in the hospitalized COVID-19-infected pregnant women group compared with the other groups ($p < 0.001$).

Discussion

To the best of our knowledge, diaphragmatic function in fetuses with COVID-19-infected mothers has not been examined. Hence, in the current study, we examined the effects of maternal COVID-19 infection on fetal diaphragm thickness and diaphragmatic excursion, which show the quality of diaphragmatic contractions. The key findings of our study were that (1) fetal diaphragmatic excursion that is primarily related to respiratory effort was significantly decreased in hospitalized COVID-19-infected mothers compared with the other groups. We can speculate that moderate COVID-19 infection adversely affected the fetal diaphragm function and fetal respiratory quality; (2) fetal diaphragmatic thicknesses and fetal costophrenic angle during both inspiration and expiration were similar among the groups; and (3) NICU requirement was significantly increased in hospitalized COVID-19-infected mothers compared with the other groups.

In the literature, there are only two studies evaluating COVID-19 infection effects on fetal lungs. In a prospective case–control study by Turgut et al, fetal pulmonary artery Doppler parameters were compared between 41 pregnant women with COVID-19 infection and 43 healthy controls. In this study, the mean gestational age at ultrasound examination was approximately 32 weeks. They reported that fetal pulmonary peak systolic velocity was increased and pulsatility indices, fetal pulmonary acceleration time, ejection time, and acceleration to ejection ratio (PATET) were decreased in COVID-19-infected mothers compared with the control group.[13] In another prospective study by Sule et al, they clarified COVID-19 infection effects on fetal lungs with fetal pulmonary acceleration time, ejection time, and PATET by comparing 55 COVID-19-infected with 93 healthy pregnant women. In this study, the mean gestational age at ultrasound examination was ~34 weeks. They reported that acceleration time was significantly increased in infected patients, but ejection time and PATET were statistically similar among the groups. In addition, they declared that 11 neonates required the NICU in the disease group, and all

Table 2 Comparision of fetal diaphragmatic thickness and diaphragmatic excursion parameters among the groups

	Control group ($n=48$)	Common cold (COVID-19 PCR negative) ($n=48$)	Outpatient COVID-19-infected group (mild) ($n=48$)	Hospitalized COVID-19-infected group (moderate) ($n=48$)	*p*-Value
Gestational age at ultrasound examination (wk)	34 (33–35)	34 (32–35)	35 (33–35)	34 (33–35)	0.740
Diaphragm thickness at inspiration (mm)	1.84 ± 0.27	1.90 ± 0.28	1.82 ± 0.22	1.79 ± 0.22	0.450
Diaphragm thickness at expiration (mm)	1.64 ± 0.20	1.64 ± 0.18	1.68 ± 0.20	1.59 ± 0.18	0.680
Diaphragmatic excursion (mm)	4.92 ± 0.70[a]	4.86 ± 0.74[a]	4.90 ± 0.68[a]	4.36 ± 0.51[b]	<0.001
Costophrenic angle at inspiration (deg)	51.4 ± 6.43	49.0 ± 7.0	53.8 ± 6.9	52. 3 ± 6.11	0.280
Costophrenic angle at expiration (deg)	38.9 ± 6.1	40.1 ± 6.5	40. 8 ± 5.9	37.1 ± 5.9	0.390

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.
Note: Different superscripts mean statistically significant.

Doppler parameters (acceleration time, ejection time, and PATET) were decreased in these neonates compare with other neonates.[14] In addition to these two studies, to the best of our knowledge, this is the first study to examine the fetal diaphragm in the presence of COVID-19 infection.

In the current study, we found that fetal diaphragmatic excursion significantly decreased in the hospitalized COVID-19-infected pregnant women without affecting fetal diaphragmatic thickness. In addition, we found that an NICU requirement was significantly increased in neonates affected by moderate COVID-19 infection compared with the other groups.

The clinical importance of ultrasonographic evaluation of the diaphragm has been clearly demonstrated in the literature. A sonographic study by Matamis et al shows diaphragmatic excursion is representative of the respiratory effort during breathing.[15] These findings are clinically important because one of the most oxygen-sensitive regions in the central nervous system is the area that coordinates diaphragmatic movements and fetal breathing. Regulatory centers can adapt their responses to hypoxemia by increasing oxygen concentration. We can explain our results with hypoxemia and fetal inflammatory response. COVID-19 infection causes a multisystemic infectious disease that also may cause fetal harm through vertical transmission. Patients may experience severe hypoxia when the virus induces acute severe pneumonia. In adition, it is well documented that the virus causes villitis, inflammation, and arteriopathy in the placenta. Furthermore, virions have been detected on placental villi.[16,17] Maternal COVID-19 infection often causes fetal distress and preterm birth, and fetal pulmonary status has become a key component in treating these complications. Maternal COVID-19 complications adversely affect fetal pulmonary circulation due to hypoxia, impaired coagulation cascades and increased cytokine levels.[18,19] A recent case report indicates that COVID-19 causes fetal inflammatory response syndrome.[20] Intrauterine infection and inflammation alter fetal lung development.[21] Surfactant lipids, which improve lung compliance, are produced by microorganisms.[22] The increased blood flow toward fetal lungs may be explained by this inflammatory process.

Strengths and Limitations

Our study has some clinical importances, and the main strengths of the current study were its prospective design and novelty. Additionally, we investigate the relationship of fetal diaphragmatic changes with the severity of the disease and most importantly, the change in the presence of viral infections (common cold) other than COVID-19. This subgroup analysis explains the effects of the disease on the fetal diaphragm more clearly and makes our study more specific. NICU admission due to respiratory morbidity increase in COVID-19-infected mothers. In these fetuses, examination fetal diaphragmatic excursion before delivery can be a noninvasive and simple method to predict NICU admission. In the presence of decreased fetal diaphragmatic excursion, corticosteroids can be administered to assist fetal lung maturation, which can decrease respiratory morbidity. Sotiriadis et al compared prophylactic corticosteroid administration prior to term elective cesarean sections with the standard protocol without corticosteroids and assessed the effect on neonatal respiratory morbidity or complications and NICU or special neonatal care unit admissions.[23] This new protocol decreased the risk of transient tachypnea of the newborn, respiratory distress, admission to the NICU, and respiratory complications requiring admission to neonatal special care and reduced the time in the NICU.[23] In the current study, patients receiving betamethasone due to preterm delivery were excluded because betamethasone is a corticosteroid that can affect the diaphragm muscle. Further prospective studies to evaluate betamethasone effects on the fetal diaphragm in COVID-19-infected mothers can open new horizons.

Although this study has clinical importance, we are aware that there are some limitations. Presenting single-center findings are limitations of the study. In our clinic, umbilical artery blood gas measurement is performed only for high-risk pregnant women in line with the American College of Obstetricians and Gynecologists guidelines. Since blood gas measurements are not routinely performed for uncomplicated and healthy infants, we do not have blood gas results for all infants. Of course, this situation raises questions regarding the relationship between blood gas parameters and fetal diaphragm measurements. Thus, new studies in which fetal blood gas results are added are eagerly anticipated. Finally, in our study, we had a few pregnant women who were diagnosed with severe COVID-19 infection and needed care in an intensive care unit during this period, but most of them progressed with maternal mortality. Therefore, the effect of severe COVID-19 infection on the fetal diaphragm could not be evaluated.

Conclusion

Our results indicated that COVID-19 infection decreased fetal diaphragmatic excursion, and ultrasonographic evaluation of fetal diaphragmatic excursion before delivery can provide important information to predict whether infants will require NICU hospitalization.

Authors' Contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Ethical Approval

The local Institutional Review Board deemed the study exempt from review.

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None.

Conflict of Interest

None declared.

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