

# Relationship Between Fetal Right Heart Doppler Findings with Lamellar Body and Fetal Lung Maturity

## Fetal Sağ Kalp Doppler Bulguları ile Lamellar Body ve Fetal Akciğer Olgunlaşması Arasındaki İlişki

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### ABSTRACT

**Aim:** The aim of this study was to investigate the effectiveness of fetal right heart doppler findings in determining pulmonary maturity.

**Materials and Methods:** The study focused on women with late preterm and term pregnancies. The main measurements included the doppler findings of the main pulmonary artery and the right pulmonary artery, as well as the E/A wave ratio of the mitral valve, which represents the ratio of peak blood flow velocity during left ventricular relaxation in early diastole to peak velocity during late diastole caused by atrial contraction, and the lamellar body count.

**Result:** We observed a significantly higher mean number of lamellar body count in the control group ( $84.70 \pm 42.77$ ) compared to the study group ( $41.21 \pm 34.81$ ). Additionally, we noticed that the systolic-diastolic ratio (S/D) of the MPA and RPA was significantly higher in the preterm group ( $7.8 \pm 1.9$ ,  $7.4 \pm 1.2$ ) compared to the term group ( $6.7 \pm 1.3$ ,  $6.1 \pm 1.6$ ). However, we did not find any significant difference in the pulsatile index and resistance indices of RPA and MPA, as well as the acceleration/ejection time ratio. The mitral valve E/A ratio was also significantly lower in the study group compared to the control group ( $p = 0.032$ ).

**Conclusion:** We observed that the systolic-diastolic ratio of the main pulmonary artery and right pulmonary artery was significantly higher in preterm cases (study group). Fetal lung maturity can be non-invasively assessed using Doppler ultrasonography.

**Keywords:** Pulmonary maturation, doppler ultrasonography, lamellar body, preterm birth, fetal pulmonary artery

### ÖZ

**Amaç:** Bu çalışmanın amacı fetal sağ kalp doppler bulgularının pulmoner olgunluğu belirlemedeki etkinliğini araştırmaktır.

**Gereç ve Yöntemler:** Çalışma geç preterm ve term gebelikleri olan kadınlara odaklanmıştır. Ana ölçümler arasında ana pulmoner arter ve sağ pulmoner arterin doppler bulguları, ayrıca mitral kapağın E/A dalga oranı (sol ventrikül gevşemesinin erken diyastolde en yüksek kan akım hızının atriyal kasılmanın neden olduğu geç diyastoldeki en yüksek hız oranını temsil eder) ve lameller cisimcik sayısı yer almaktadır.

**Sonuç:** Kontrol grubunda ( $84.70 \pm 42.77$ ) çalışma grubuna ( $41.21 \pm 34.81$ ) kıyasla anlamlı derecede daha yüksek ortalama lameller vücut sayısı gözlemledik. Ek olarak, MPA ve RPA'nın sistolik-diastolik oranının (S/D) preterm grubunda ( $7.8 \pm 1.9$ ,  $7.4 \pm 1.2$ ) term grubuna ( $6.7 \pm 1.3$ ,  $6.1 \pm 1.6$ ) kıyasla anlamlı derecede daha yüksek olduğunu fark ettik. Ancak, RPA ve MPA'nın pulsatil indeksi ve direnç indekslerinde ve ivme/ejeksiyon zamanı oranında anlamlı bir fark bulamadık.

**Sonuç:** Ana pulmoner arter ve sağ pulmoner arterin sistolik-diastolik oranının preterm vakalarda (çalışma grubu) anlamlı derecede daha yüksek olduğunu gözlemledik. Fetal akciğer olgunluğu, Doppler ultrasonografi kullanılarak invaziv olmayan bir şekilde değerlendirilebilir.

**Anahtar Kelimeler:** Akciğer maturasyonu, doppler ultrasonografi, lameller cisim, preterm doğum, fetal pulmoner arter

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## INTRODUCTION

Preterm labor (PL) is defined as the onset of labor before the 37th week of gestation, and it is a leading cause of neonatal mortality due to premature birth and associated morbidity (1). The incidence of preterm labor affects between 5 to 10% of all pregnancies. The main reasons for perinatal mortality and morbidity are complications associated with preterm labor (2). In this situation, the survival of infants leads to the emergence of medical and economic challenges.

The primary goal is to prevent preterm labor and accurately evaluate lung maturity. Although there is no cure for preterm labor, there are ways to delay it to give the baby's lungs more time to mature. Various tests have been created to precisely assess lung maturity. These tests involve evaluating the biochemical compounds and physical properties of the amniotic fluid, as well as counting the lamellar bodies (3).

Doppler ultrasonography is a fast, reliable, and non-invasive technique used to evaluate fetal and maternal physiology and pathophysiology. As the pregnancy progresses, fetal pulmonary resistance decreases, and blood flow is expected to increase (4). It seems that the findings from the fetal right heart doppler could be helpful in predicting fetal lung maturation. This study seeks to analyze the data from the fetal main pulmonary artery (MPA) and right pulmonary artery (RPA), as well as the mitral valve E/A wave in late preterm cases, and then compare the findings with those in term cases.

## MATERIAL AND METHODS

This study is a prospective clinical study and was initiated after receiving approval from the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee, numbered 2017/88. The sample size was determined based on the number of eligible patients who met the inclusion criteria within the study period (2017–2019). A formal sample size calculation was not performed due to the exploratory nature of the study. However, the sample size was deemed sufficient for initial hypothesis testing based on prior similar studies in the literature.

Between 2017 and 2019, the study included pregnant women admitted to the Department of Obstetrics and Gynecology at Karadeniz Technical University. The research focused on instances of cesarean section performed after the 34th week of pregnancy. The study included cases with a diagnosis of preterm labor and a cesarean indication, such as fetal distress or a previous cesarean birth. Pregnant women with pregestational or gestational diabetes mellitus, morbid obesity, thyroid dysfunction, fetal anomaly,

aneuploidy, and multiple pregnancies were excluded from the study. Demographic data, ultrasonographic data, and doppler parameters of all patients were recorded and evaluated prospectively. Informed consent was obtained from all participants before their involvement. The results of the newborn after birth were also documented. Prenatal corticosteroid administration was given to preterm cases to prevent newborn tachypnea, as per the guidelines.

Patients were divided into two groups: the study group included late preterm cases (34 0/7-36 6/7 weeks of gestation), and the control group included term cases (>37 weeks of gestation).

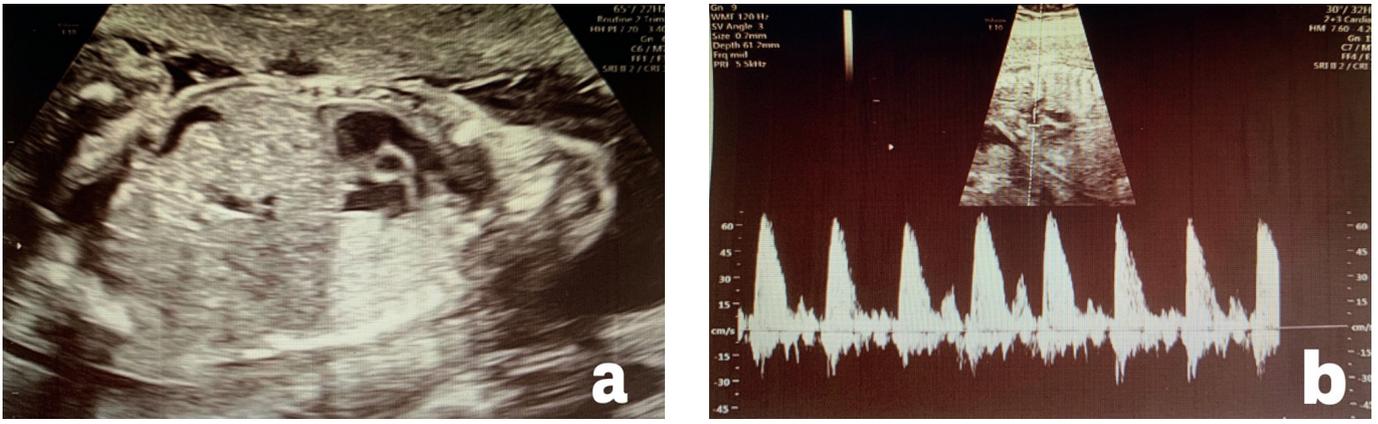
Doppler data from the main pulmonary artery and right pulmonary artery, as well as the mitral valve E/A wave ratio and lamellar body count, were identified as the primary research parameters. In both groups, the fetal thorax and heart circumference ratios, mitral E/A wave ratio, right pulmonary artery, and main pulmonary doppler indexes PI, RI, S/D, AT/ET were assessed before the cesarean section. Ultrasonographic examinations and measurements were conducted by a single certified perinatologist using a Voluson Expert 730 color Doppler ultrasonography device (GE). Doppler measurements were conducted with the individuals lying in a slightly left-facing supine position. Doppler index measurements for each pregnant individual in both groups were recorded separately.

The main pulmonary artery was observed at the right ventricular outlet in the sagittal section (Figure 1-a), and measurements were made on the midline of the pulmonary valve with an angle of insonation below 10 degrees (Figure 1-b). In the sagittal section, we followed the right pulmonary artery and the main pulmonary artery, and took a measurement just after the pulmonary artery split, at an angle of insonation less than 10 degrees (Figure 2). The evaluation of the mitral valve E and A can be seen in Figure 3.

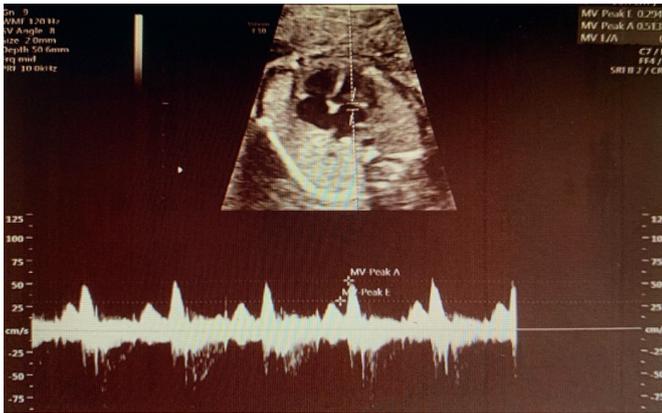
### Lamellar Body Count(LBC);

During the cesarean section, at least 2cc of amniotic fluid that was not contaminated with blood was taken into an EDTA tube and not centrifuged. Immediately after the uterine incision, the uncontaminated amniotic fluid was aspirated and transferred to a tube for lamellar counting. The sample was analyzed using an automatic blood counting device, specifically a Coulter Counter, which is commonly used in hematology laboratories for counting blood elements. The number of lamellar bodies was reported as the platelet count. The results are expressed in units of  $\times 10^3 \mu 1$ .

Note: In our methodology, the amniotic fluid was directly analyzed without dilution or centrifugation. We acknowledge that some laboratories may recommend mixing the sample with specific solutions prior to analysis; this variation in methodology has been added to the Discussion as a consideration.



**Figure 1.** a. Doppler view of the main pulmonary artery on sagittal section, b. Doppler view of the main pulmonary artery acceleration / ejection time on sagittal section



**Figure 2.** Doppler view of the right pulmonary artery immediately after the pulmonary artery bifurcation on sagittal section at a 10-degree insonation angle.



**Figure 3.** Doppler view of mitral valve e, a wave.

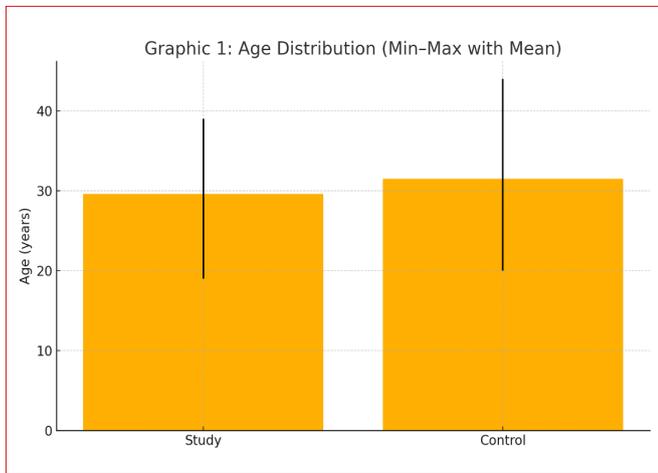
### Statistical analysis

Data were analyzed using IBM SPSS Statistics 11 (IBM SPSS, Turkey). Normality of data distribution was assessed using the Shapiro–Wilk test. For normally distributed continuous variables, comparisons between the two groups were made using Student's t-test. For variables that were not normally distributed, the Mann–Whitney U test was applied. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Results are expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range, IQR), depending on distribution. A p-value  $<$  0.05 was considered statistically significant.

### RESULTS

A total of 70 pregnant women (n: 70) participated in the study, with 25 in the study group and 45 in the control group. Upon analyzing the demographic characteristics, it was determined that the study group's patients had a minimum age of 19, a maximum age of 39, and a mean age of  $29.6 \pm 6$  years. In comparison, the control group had a minimum age of 20 years, a maximum age of 44, and a mean age of  $31.5 \pm 5.9$  years (Graphic 1). The mean number of gravida was  $2.84 \pm 2.01$  in the study group and  $3.34 \pm 1.38$  in the control group. Similarly, the average values for parity were  $1.52 \pm 1.71$  in the study group and  $1.89 \pm 1.12$  in the control group. The average values for abortion were  $0.28 \pm 0.45$  in the study group and  $0.50 \pm 0.69$  in the control group (Table 1).

In the study group, the birth weights of newborns ranged from 1450g to 3600g, with a mean birth weight of  $2570.63 \pm 574.18$  g. In the control group, the birth weights ranged from 2200g to 4380g, with a mean birth weight of  $3282.85 \pm 501.38$  g (Graphic 2).



**Graphic 1.** Distribution of maternal age in the study and control groups, represented with mean values and error bars indicating minimum and maximum ranges.

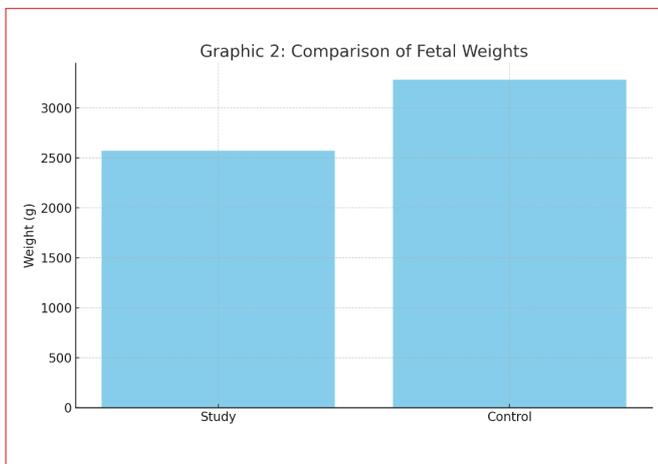
When analyzing the distribution of neonatal gender, there were 15 male newborns and 10 female newborns in the study group. In the control group, there were 18 male newborns and 27 female newborns (Graphic 3).

Respiratory distress syndrome (RDS) complications were observed in 5 (11.2%) of the newborns in the control group (n=45) and 7 (28%) in the study group (n=25). Tachypnea was noted in 17 (68%) of the newborns in the study group (n=25) and in 8 (20%) in the control group (Table 2).

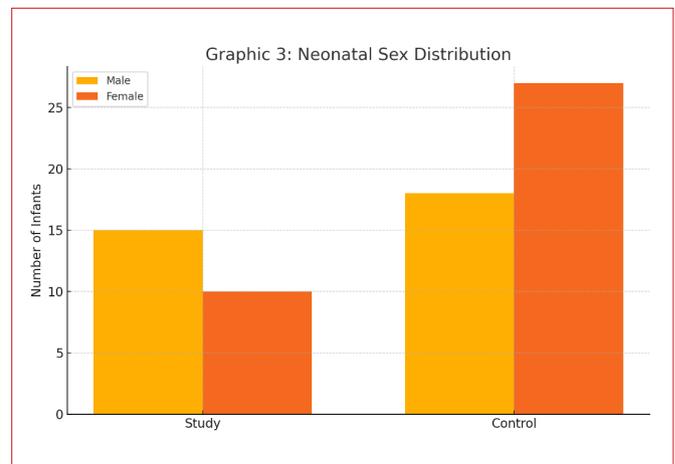
During the cesarean section, amniotic fluid was collected from both groups. The count of lamellar bodies in the fluid was determined. In the study group, the minimum value was  $2 \times 10^3$ , the maximum value was  $132 \times 10^3$ , and the mean value was  $41.21 \pm 34.81 \times 10^3$ . In the control group, the minimum value was  $25 \times 10^3$ , the maximum

**Table 1.** Demographic characteristics of both groups

Parameter	Study Group (Mean $\pm$ SD / Median [IQR])	Control Group (Mean $\pm$ SD / Median [IQR])	Min - Max	p-value (Test)
Age (years)	29.6 $\pm$ 6	31.5 $\pm$ 5.9	19-39 / 20-44	0.19 (Student's t-test)
Gravida	2.84 $\pm$ 2.01	3.34 $\pm$ 1.38	1-9 / 1-7	NS
Parity	1.52 $\pm$ 1.71	1.89 $\pm$ 1.12	0-6 / 0-5	NS
Abortion	0.28 $\pm$ 0.45	0.50 $\pm$ 0.69	0-1 / 0-3	NS



**Graphic 2.** Comparison of mean fetal birth weights between the study group (late preterm) and control group (term).



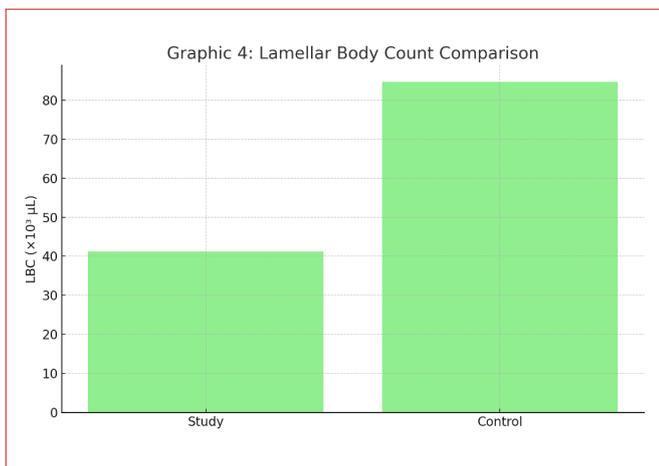
**Graphic 3.** Distribution of neonatal sex (male/female) in both the study and control groups.

**Table 2.** Newborn outcomes and fetal characteristics

Parameter	Study Group	Control Group	Values	p-value (Test)
Fetal Sex (M/F)	15/10	18/27	Number	Descriptive
Fetal Weight (g)	2570.63 $\pm$ 574.18	3282.85 $\pm$ 501.38	Mean $\pm$ SD	Not specified
RDS (n/%)	7 / 28%	5 / 11.2%	Number / %	Descriptive
Tachypnea (n/%)	17 / 68%	8 / 20%	Number / %	Descriptive

**Table 3.** Doppler findings and LBC values with statistics

Parameter	Study Group (Mean ± SD)	Control Group (Mean ± SD)	95% CI (Mean Diff.)	p-value (Test)
LBC ( $\times 10^3 \mu\text{L}$ )	41.21 ± 34.81	84.70 ± 42.77	[20.69 – 66.29]	0.000 (Student's t-test)
MPA PI	2.275 ± 0.2579	2.219 ± 0.3019	[-0.22 – 0.11]	0.50 (Student's t-test)
MPA RI	0.853 ± 0.0497	0.848 ± 0.0477	[-0.03 – 0.01]	0.66 (Student's t-test)
MPA AT/ET	0.304 ± 0.0924	0.288 ± 0.0881	[-0.06 – 0.03]	0.49 (Student's t-test)
MPA S/D	7.8 ± 1.9	6.7 ± 1.3	[-1.91 – -0.23]	0.013 (Student's t-test)
RPA PI	2.447 ± 0.3002	2.258 ± 0.4439	[-0.44 – 0.06]	0.14 (Student's t-test)
RPA RI	0.847 ± 0.0547	0.818 ± 0.0644	[-0.06 – 0.008]	0.12 (Student's t-test)
RPA AT/ET	0.331 ± 0.0890	0.310 ± 0.1120	[-0.08 – 0.041]	0.49 (Student's t-test)
RPA S/D	7.4 ± 1.2	6.1 ± 1.6	[-2.15 – -0.33]	0.008 (Student's t-test)
Mitral E/A	0.689 ± 0.0993	0.740 ± 0.0865	[0.004 – 0.09]	0.032 (Student's t-test)
Heart/Thorax Ratio	0.588 ± 0.0573	0.593 ± 0.0478	[-0.02 – 0.03]	0.70 (Student's t-test)

**Graphic 4.** Comparison of mean lamellar body counts (LBC) between the study and control groups.

value was  $209 \times 10^3$ , and the mean value was  $84.70 \pm 42.77 \times 10^3$ . The mean number of lamellar bodies was significantly higher in the control group compared to the study group ( $p = 0.01$ ) (Graphic 4).

The study group showed significantly higher S/D ratios of the main pulmonary artery ( $7.8 \pm 1.9$ ) compared to the control group ( $6.7 \pm 1.3$ ) ( $p = 0.013$ ). Additionally, the MPA PI was  $2.275 \pm 0.2579$  in the study group and  $2.219 \pm 0.3019$  in the control group ( $p = 0.509$ ). The RI was  $0.853 \pm 0.049$  in the study group and  $0.848 \pm 0.0477$  in the control group ( $p = 0.665$ ). Furthermore, the study group exhibited a higher AT/ET ratio ( $0.304 \pm 0.092$ ) compared to the control group ( $0.288 \pm 0.0881$ ) ( $p = 0.496$ ); however, this difference was not statistically significant (Table 3).

The systolic/diastolic ratios of the right pulmonary artery were found to be significantly higher in the study group ( $7.4 \pm 1.2$ ) compared to the control group ( $6.1 \pm 1.6$ ) ( $p = 0.008$ ). Additionally, the RPA PI

were  $2.447 \pm 0.3002$  and  $2.258 \pm 0.4439$  ( $p = 0.148$ ) for the study and control groups, respectively. The RI were  $0.847 \pm 0.0547$  and  $0.818 \pm 0.0644$  ( $p = 0.1123$ ) for the study and control groups. The AT/ET ratio was higher in the study group ( $0.331 \pm 0.890$ ) than in the control group ( $0.310 \pm 0.112$ ) ( $p = 0.493$ ), but this difference was not statistically significant.

The study group had significantly lower ratios of mitral valve E/A ( $0.689 \pm 0.0993$ ) compared to the control group ( $0.75 \pm 0.087$ ) ( $p = 0.032$ ). In terms of the ratio of heart circumference to thorax circumference, the preterm group had a higher ratio ( $0.59 \pm 0.058$ ) compared to the term group ( $0.6 \pm 0.048$ ), although no statistical difference was found.

## DISCUSSION

This study has several limitations that must be considered when interpreting the results. These include the relatively small and unequal group sizes, lack of blinding for the operator, and selection bias from including only cesarean deliveries after 34 weeks, which may not represent the full spectrum of preterm pathology. No adjustment for multiple comparisons was made, increasing the possibility of Type I error. Although statistically significant differences in Doppler indices were found, the clinical significance of these findings remains uncertain. Furthermore, the LBC count is known to be affected by gestational age, which may have influenced our results. We did not perform multivariate analysis to control for confounders such as corticosteroid exposure or underlying maternal conditions. Future studies should include larger sample sizes, correction for gestational age, and multivariate analyses to better understand these relationships.

Preterm birth occurs between fetal viability and completion of 37th week of pregnancy, categorized as preterm, term, or postterm based on gestational age (1). Prematurity and its challenges account for 83-85% of deaths unrelated to fetal anomalies in the neonatal period(5). Premature newborns are at risk for specific diseases due to the immaturity of various organ systems. The most important problems include RDS, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, patent ductus arteriosus (PDA), hyperbilirubinemia, prolonged phototherapy or exchange transfusion, hypoglycemia, hypocalcemia, retinopathy, and bronchopulmonary dysplasia (6).

The problems such as RDS, IVH, and NEC that occur in the early period are more common in premature babies compared to term babies (6). Late-onset problems such as cerebral palsy (CP), visual disturbances, and hearing loss are more common in preterm infants (7).

In the case of an unavoidable premature birth, the first concern is whether the baby's lungs have matured. Various tests have been developed to expedite lung maturation or accurately assess fetal lung maturity during this critical stage.

Assessing physical properties (TDx-FLM II assay), measuring biochemical compounds (such as phosphatidylglycerol and lecithin/sphingomyelin ratio), and directly counting lamellar bodies in amniotic fluid can help predict fetal lung maturation. These tests have been used in clinical practice for many years, but they are not perfect and may have margins of error. Additionally, obtaining amniotic fluid, which is necessary for these tests, involves an invasive procedure. Some of these tests are time-consuming, expensive, require specialized technology, and trained personnel. Therefore, there is a growing need for diagnostic methods that are affordable, easy to perform, quick, require no specialized technology or personnel, and are more reliable. The counting of lamellar bodies in amniotic fluid is an important test and is recommended as a gold standard test in some sources. Many laboratories use the LBC method to evaluate fetal lung maturation. Blood counters in hematology laboratories can easily count lamellar bodies, which are of similar shapes and sizes as platelets. The method provides a simple, fast, and inexpensive assessment compared to other methods (8).

Doppler ultrasound is a crucial diagnostic tool for assessing high-risk pregnancies. It measures maternal and fetal doppler velocimetry to predict fetal well-being and evaluate blood flow non-invasively. In 1977, Fitzgerald and Drumm conducted the first studies on using doppler in obstetrics and gynecology. This method examines various vessels, including the umbilical artery, maternal uterine artery, fetal cerebral arteries, and aorta to assess blood flow in the fetomaternal circulation during pregnancy. The

use of Doppler in obstetrics is expanding, allowing the examination of many veins. The efficiency of doppler ultrasonography as an alternative to invasive tests for early and accurate determination of lung maturation in premature births and its complications is still debated. Current procedures for detecting fetal lung maturation necessitate invasive interventions. In this study, we evaluated right heart doppler data along with the lamellar body count, which is a gold standard method for determining lung maturation.

We examined fetal MPA and RPA Doppler data as well as the mitral valve e/a wave in late preterm and term cases. We compared the results between both groups. In our study, we found that the S/D ratios of MPA and RPA Doppler indices were significantly higher in the study group than in the control group. Additionally, PI, RI, and AT/ET indices were found to be increased in the study group compared to the control group, but this difference was not statistically significant. The mitral valve e/a ratios were significantly lower in the study group than in the control group. Moreover, the ratio of heart circumference to thorax was higher in the preterm group than the term group, and this difference was not statistically significant. Finally, the mean number of lamellar bodies was significantly higher in the control group than in the study group.

During gestation, lung development progresses, but pulmonary vascular resistance increases while pulmonary artery vascular resistance decreases slightly. Research has shown that the waveforms of the fetal pulmonary artery change as gestational age advances. Guan et al. conducted a study to examine the impact of gestational age on the main pulmonary artery doppler waveforms. The AT/ET ratio increased significantly as gestational age increased. The PSV, EDV, and MV also showed a significant but less pronounced increase with gestational age. The PI was inversely linearly correlated with gestational age, while ET and RI did not change significantly throughout gestation (9). In our study, when we compared the control and study groups, we found an increase in PI and RI values in term cases.

Schenone et al. reported a positive correlation between the acceleration/ejection time ratio of the fetal main pulmonary artery Doppler waveform and the surfactant/albumin ratio assessed following amniocentesis for fetal lung maturity testing.(10). Azpurua et al. reported that as the lecithin/sphingomyelin ratio increased, the acceleration/ejection time ratio of the fetal pulmonary artery decreased, thereby reducing the likelihood of fetal lung maturity (11). Kim et al had similar results to Azpurua. They argued that the MPA AT/ET duration ratio correlated inversely with fetal lung maturation (12). MPA AT/ET ratios were  $0.304 \pm 0.092$  in our study group and  $0.28 \pm 0.08$  in our control group.

In their study, Moety et al. examined the role of main pulmonary artery doppler indices in predicting RDS and found significant findings in the MPA AT/ET ratio. They observed that fetuses with RDS had significantly lower gestational weeks. Additionally, patients with RDS had significantly higher PI and RI values. The S/D ratios were found to be high in patients with RDS, although this difference was not statistically significant (13).

In this study, one of the most significant findings was the notably higher systolic-diastolic ratio of the main pulmonary artery and right pulmonary artery in the late preterm group compared to the full-term cases. Because the S/D ratio is relatively simple to measure and is consistently linked to gestational age, we believe it can serve as a potentially useful marker for evaluating fetal lung maturation.

In summary, fetal pulmonary doppler waveforms can be measured during pregnancy to evaluate fetal pulmonary circulation. This is a safe and reproducible technique for detecting lung maturation and can be useful as a noninvasive test to identify fetuses at risk. However, larger case series and prospective clinical trials are needed to support these assessments.

**Ethics Committee approval:** Karadeniz Technical University Presidency, KTU Faculty of Medicine, Presidency of the Scientific Research Ethics Committee The study was approved with the written decision dated 28/06/2017 and numbered 24237859-402.

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**The data that support the findings of this study are openly available in Figshare, <https://figshare.com/s/4199ff8c38f1c3a4a595> at <https://doi.org/10.6084/m9.figshare.27180585>, CÖMERT, ERHAN (2024). Untitled Item. figshare.**

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