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Original Research Article

Fetal lung volume and pulmonary artery resistance index for prediction of neonatal respiratory distress syndrome

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ABSTRACT

Background: As gestational age grows, the risk of newborn respiratory distress syndrome (RDS) diminishes because the lungs are the last foetal organs to properly mature. While neonatal RDS does not just occur following preterm births, it is often thought of as a disorder of premature babies. This study sought to determine how prenatal lung capacity and foetal Pulmonary artery resistance index (PARI) affected the probability that newborn RDS would occur.

Methods: This prospective observational study was carried out on 200 pregnant women aged 20-35 years, with gestational age between 36-40 weeks and singleton pregnancy. According to neonatal outcome the patients were classified into two groups: group A: 26 cases with neonatal RDS and group B: 174 cases without neonatal RDS. All patients were subjected to 2D ultrasonography and 3D ultrasonography.

Results: Fetal lung volume (FLV) is a significant predictor of neonatal RDS (AUC: 0.820, $p < 0.001$), at a cut off value of ≤ 35 , with 88.5% sensitivity and 68.4% specificity. PARI is not a significant predictor of neonatal RDS. 1 and 5 min Apgar score were significantly lower in neonates who developed RDS and those who didn't ($p < 0.001$).

Conclusions: 3D FLV and estimated fetal weight measurement using ultrasonography may be a reliable non-invasive indicator of the incidence of newborn RDS in preterm pregnancies when the risk of RDS progression is present. FLV is a significant predictor for neonatal RDS at a cutoff for $\leq 35 \text{ cm}^3$ with sensitivity 88.5% and specificity 68.4%.

Keywords: Fetal lung volume, Pulmonary artery resistance index, neonatal respiratory distress syndrome, Fetal lung volume

INTRODUCTION

Neonatal respiratory distress syndrome (RDS) is described as respiratory failure that develops after delivery as a result of a lack of lung surfactant, a component necessary to maintain lung expansion and avoid alveolar collapse. This disorder is a major source of newborn morbidity and death.¹

Since the lungs are the last foetal organs to properly develop, the risk of newborn RDS decreases with increasing gestational age. Although neonatal RDS does not just occur following preterm births, it is often thought of as a disorder of premature babies.¹ To assist obstetricians choose when to deliver a neonate and to

assess the risk of newborn RDS, a biochemical tests have been created. The most reliable indicators of foetal lung maturity (LM) are the amniotic fluid's biological, chemical, and physical characteristics. However, the only way to acquire amniotic fluid is by the invasive technique of amniocentesis, which has the potential to threaten the pregnancy by causing premature membrane rupture, placental abruption, preterm labour, fetomaternal bleeding, foetal injury, or even foetal or maternal mortality.²

For pregnant women, a non-invasive method to check foetal LM would be a better alternative. Indirect measurements of foetal LM have been made using Doppler blood flow waveforms and ultrasonic examination of gross

morphology.^{3,4} But as of yet, there is no trustworthy non-invasive technique to anticipate foetal LM before to birth.^{5,6} Neonatal RDS may be predicted using measurements of foetal lung volume (FLV) and pulmonary artery Doppler. With growing gestational age, the foetal lung's structural and functional development advances, which changes the organ's sonographic echogenicity characteristic.^{7,8} Additionally, it was shown that foetal pulmonary artery flow velocity waveforms changed as gestational age increased.⁹ The aim of the study was to assess how the prenatal lung capacity and foetal pulmonary artery resistance index affected the probability that the newborn RDS would emerge.

METHODS

This prospective observational study was carried out on 200 pregnant women aged 20-35 years, with gestational age between 36-40 W and singleton pregnancy.

An informed written consent was obtained from the patients. After receiving authorization from Tanta University's Ethical Committee, the research was carried out.

Individuals with uncertain gestational age, congenital foetal anomalies, intrauterine growth restriction, placental abnormalities, macrosomia, as well as any illnesses associated with pregnancy (such as preeclampsia, hypertension, or diabetes mellitus), autoimmune conditions, and morbid obesity were all excluded.

According to neonatal outcome the patients were classified into two groups: group A: 26 cases with neonatal RDS and group B: 174 cases without neonatal RDS

All patients were subjected to personal data, complete history taking, 2D ultrasonography and 3D ultrasonography.

2D ultrasonography¹⁰

Bi-parietal diameter (BPD) was determined along a line perpendicular to the direction of the cerebral falx, from the outer border of the proximal parietal bone to the inner wall of the distal skull table. On a transverse view of the foetal abdomen, the abdominal circumference (AC) was calculated at the level of the meeting of the umbilical vein, portal sinus, and foetal stomach when it was obvious. The measurement was taken at the level of the skin line.

Femur length (FL) measurement was obtained from one side of diaphysis to the other. Epiphyseal ossification centers: In the axial plane, the femur's echogenic distal epiphyseal centre was discovered and assessed. In addition, the proximal echogenic tibial epiphysis centre may be detected towards the end of the tibia. We once again took measurements in the axial (antero-posterior) plane.

Grading the placenta: grading was carried out in accordance with the grannum classification: grade 0 refers to an evenly calcified chorionic plate, grade 1 refers to an undulated chorionic plate with dotted calcifications, grade 2 refers to an incomplete single line of calcification that does not touch the basal plate, and grade 3 refers to an indentation and calcification of the chorionic plate that reaches the basal plate.¹⁰

Amniotic fluid index and free-floating particles¹¹

The four-quadrant approach was used to estimate the amniotic fluid index (AFI), which was determined by measuring each fluid pocket's unobstructed, deepest, vertical length in centimetres in each quadrant. AFI typically fell between 8 and 18. Four quadrants of the amniotic fluid were identified to have linear densities (Vernix), which were measured in millimetres. Depending on the size, quantity, and dispersion of the free-floating particles in the four quadrants, the turbidity of the amniotic fluid was determined. After a light probing shake of the mother's belly, they were identified by their freedom of movement.

3D ultrasonography

Obstetric ultrasonography was performed using the Samsung medison H60, KOREA and 50/60HZ transabdominal probe) on admission. To calculate FLV, three-dimensional ultrasonography was used.

A longitudinal section of the foetal chest was taken; a 3D window was triggered, accompanied by an electrical scan of the whole body. The scan was redone if any foetal movements or excessive mother breathing were seen during this sweep that would have affected the accuracy of the image.

After starting the virtualized organ computer-aided analysis (Vocal) application, the manual choice with 30° rotation steps was selected. The 3D multiplanar view's active box was determined to be box (A). The lung was drawn from its apex to its base.

FLV was automatically calculated for each lung following six rotations across a longitudinal axis. The two volumes' average was computed. The same operator measured FLV three times, and the average of those measurements was noted. After getting the transverse slice of the foetal chest, the standard three vessel and four chamber views of the heart were always acquired. A three-vessel image of the foetal heart was acquired to calculate PARI. The sample volume was concentrated on the pulmonary artery root, and pulsed Doppler was employed.

Due to the blue and red colours' tendency to overlap, colour Doppler was not employed since it would have obscured the foetal pulmonary artery. Pulsed Doppler, which lacks colour, was thus selected. Based on the sonographic anatomy, the sample volume was just above

the artery. After employing the marker at peak systole and end diastole, the computerised device immediately estimated umbilical artery RI.

Sample size calculation

The sample size for this study was calculated according to Arkin, 1984 using the following equation:

$$N = \frac{(Z_{\alpha})^2}{d}$$

N= total sample size, Z α = is standard normal variant and it is equal 8.74 at p<0.05, SD= standard deviation of variable, d= absolute error or precision.

Statistical analysis

The SPSSv25 statistical analysis programme was used. The mean and standard deviation (SD) of quantitative variables were reported, and they were compared for the same group using a paired Student's t-test. Frequency and percentages (%) were used to illustrate qualitative variables. Analyzing the sensitivity, specificity, positive, and negative predictive values (PPV and NPV) as a diagnostic performance. Agreement of the paired student's t test was used to compare the readings of TTE and EC. Between TTE and EC, bias and its standard deviation were estimated. TTE and EC readings' modified Bland Altman plots were generated. Significant results were defined as two tailed p values of less than 0.05.

RESULTS

Table 1 shows baseline characteristics of the study participants. Neonates with RDS did not significantly vary from those without in terms of mother age or delivery method. Neonatal RDS cases had substantially younger gestational ages than controls (p=0.018). Both infants who had RDS and those who did not had substantially decreased EFW and FLV values (p<0.001). Neonates with RDS did not significantly vary from those without it in terms of PARI (Table 2).

Neonatal birth weight was significantly lower neonates who had RDS and those who hadn't (p<0.001). 1 and 5 min Apgar score were significantly lower in neonates who had RDS and those who hadn't (p<0.001). Number of neonates with 1 and 5 min Apgar score less than 7 was significantly higher in neonates who developed RDS and those who didn't (p<0.001) (Table 3). There was no significant difference in PARI between patients with 1 min Apgar score <7 or \geq 7. FLV was significantly higher in patients with 1 min Apgar score \geq 7 than patients with 1 min Apgar score <7 (p=0.005). There was no significant difference in PARI between patients with 5-min Apgar score < or \geq 7. FLV was significantly higher in patients with 5-min Apgar score \geq 7 than patients with 5min Apgar score <7 (p=0.005) (Table 4). FLV is a significant predictor of neonatal RDS (AUC: 0.820, p<0.001), at a cut off value of \leq 35 it can predict neonatal RDS with a sensitivity of 88.5%, specificity of 68.4%. PARI is not a significant predictor of neonatal RDS (Figure 1).

Table 1: Baseline characteristics, US findings neonatal outcomes and development of neonatal RDS and NICU admission of the study participants.

Maternal age (years)	Study participants (N=200) N (%)
Maternal age (years)	26.96 \pm 4.41
Gestational age (weeks)	37.84 \pm 1.22
Mode of delivery	
CS	116 (58)
Normal delivery	84 (42)
US findings	
EFW (g)	3365 \pm 275
PARI (cm/s)	0.82 \pm 0.06
FLV (cm ³)	38.16 \pm 6.88
Neonatal outcomes	
Neonatal birth weight (g)	3395 \pm 229
1 minute Apgar score	7 (7-8)
<7	47 (24)
\geq 7	153 (77)
5-minute Apgar score	8 (7-8)
<7	26 (13)
\geq 7	174 (87)
Development of neonatal RDS and NICU admission	
Neonatal RDS	26 (13)
NICU admission	26 (13)

Note: CS: Cesarean section, US: ultrasound, AFI: amniotic fluid index, EFW: estimated fetal weight, PARI: pulmonary artery resistance index, FLV: fetal lung volume, RDS: respiratory distress syndrome, NICU: neonatal intensive care unit.

Table 2: Baseline characteristics and US findings of neonates with or without RDS.

Variables	Group A (n=26)	Group B (n=174)	P value N (%)
Maternal age (years)	28.38±3.48	26.86±4.51	0.087
Gestational age (weeks)	37.31±1.05	37.91±1.23	0.018*
Mode of delivery	CS	17 (65)	99 (57)
	Normal delivery	9 (35)	75 (43)
US findings			
EFW (g)	3010.96±122.13	3418.07±251.7	<0.001*
PARI (cm/s)	0.82±0.08	0.83±0.05	0.723
FLV (cm ³)	31.81±3.46	39.11±6.76	<0.001*

Note: CS: Cesarean section, US: ultrasound, AFI: Amniotic fluid index, EFW: estimated fetal weight, PARI: Pulmonary artery resistance index, FLV: fetal lung volume, *-statistically significant as p≤0.05.

Table 3: Outcomes in neonates with or without RDS.

Variables	Group A (n=26)	Group B (n=174)	P value N (%)
Neonatal birth weight (g)	3137.65±116.9	3434.25±216.78	<0.001*
1 minute Apgar score	3 (2-4)	7 (7-8)	<0.001*
1-minute Apgar score	<7	21 (81%)	26 (15%)
	≥7	5 (19%)	148 (85%)
5-minute Apgar score	4 (3-4)	8 (7-8)	<0.001*
5-minute Apgar score	<7	26 (57%)	0 (0%)

Note: *- Statistically significant as p≤0.05. Apgar: Appearance, pulse, grimace, activity and respiration.

Table 4: US findings of neonates according to 1 min Apgar score and 5 min Apgar score.

Variables	1 min Apgar score<7 (n=47)	1 min Apgar score≥7 (n=153)	P value
PARI (cm/s)	0.82±0.07	0.83±0.05	0.842
FLV (cm ³)	35.7±6.19	38.92±6.92	0.005*
5 min Apgar			
PARI (cm/s)	0.82±0.08	0.83±0.05	0.335
FLV (cm ³)	31.81±3.46	39.11±6.76	<0.001*

Note: US: Ultrasound, AFI: Amniotic fluid index, EFW: Estimated fetal weight, PARI: Pulmonary artery resistance index, FLV: Fetal lung volume, *-statistically significant as p≤0.05.

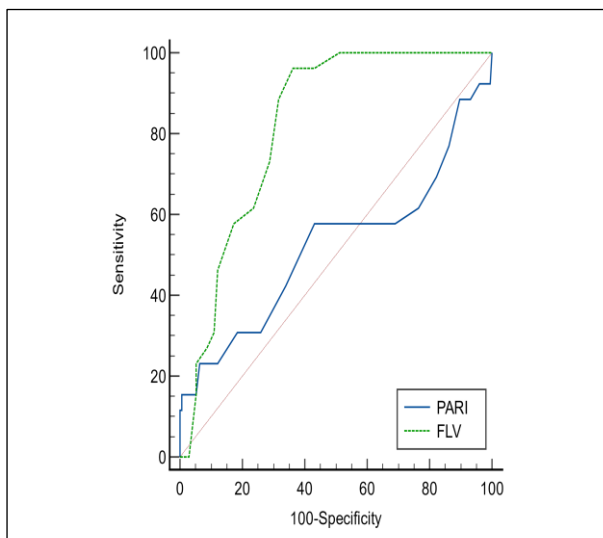


Figure 1: ROC curve analysis of PARI and FLV for prediction of neonatal RDS in the study neonates.

DISCUSSION

The purpose of our research was to assess the contribution of FLV and foetal pulmonary artery RI to the probability of newborn RDS development.

In the present study, neonatal RDS emergence and NICU admission were estimated and found that neonatal RDS occurred in 26 (13%) neonates and 26 (13%) neonates were admitted to NICU. When compared to neonates that did not have RDS, the gestational age was considerably lower in the RDS neonates (p = 0.018). Neonatals with RDS had considerably lower EFW and FLV than those without (p 0.001), but there was no other substantial difference in PARI between RDS neonates compared with no RDS neonates. FLV cm³ is a significant predictor for neonatal RDS at a cut-off for ≤35 with sensitivity 88.5 % and specificity 68.4%. Number of neonates with 1 and 5-min Apgar score less than 7 was significantly higher in neonates who developed RDS and those who didn't (p<0.001).

The present study used non-invasive sonographic technique (2D ultrasonography, 3D ultrasonography and pulsed Doppler) to determine FLM. A noninvasive test is preferred since all rely on amniocentesis, an invasive technique that has risks and consequences in approximately 0.7% of instances, including preterm labour, placental abruption, premature rupture of membranes, and fetomaternal haemorrhage.¹²

Abdelmagied et al conducted their prospective cohort study to investigate the role that FLV, PARI, and adrenal gland volume (AGV) play in the prognosis of RDS in diabetic pregnancies.¹³ According to the findings, RDS was more likely to occur in neonates with FLV of 28.4 or lesser and PARI of 0.85 or higher. In comparison to using either measure alone, a predictive model that included both FLV and PARI had higher accuracy (89.7%) and NPV (89.2%).

In order to establish standard cutoff values for average FLV and PARI for predicting the newborn RDS in low-risk term pregnancies, Laban et al conducted cross-sectional research on 80 women aged 20 to 35 years. The findings showed that in low-risk term pregnancies, FLV (cut-off ≤ 32 cm³) and PARI (cut-off ≥ 0.74) were accurate predictors of newborn RDS.¹⁴ Both of these studies were different from the current research in that there was no significant difference in PARI between RDS neonates compared with not RDS neonates. Maged et al emphasised that foetuses with RDS have considerably smaller 3D FLVs.¹⁵ With a frequency that is inversely correlated to gestational age (up to 30% in neonates born before 28 weeks and 5% in those born over 34 weeks), RDS is the most prevalent cause of newborn respiratory distress. Lung immaturity, either structurally or functionally, has been linked to the underlying process.

According to Prendergast et al, 3D FLVs may be helpful in predicting the prognosis of the newborn respiratory system in foetuses with impaired lung growth (with CDH and with anterior wall defects).¹⁶

Additionally, Laban et al discovered that whereas PARI was considerably greater in neonates who did not have RDS ($p = .02$), FLV was considerably lower in those who did ($p = .04$). Cut-off levels of FLV ≤ 27.2 cm³ and PARI ≥ 0.77 anticipated the emergence of RDS in the future. Combining the two cut-offs resulted in a systematic strategy that was more sensitive and specific for the prediction of RDS (sensitivity 100%, specificity 88.5%).¹⁷ Guan et al reported significant correlations between gestational age and neonates with RDS.¹² Moreover, fetal (Microscopic polyangiitis) MPA Doppler waveforms illustrated that (32.6%) of neonates developed RDS. With a gestational age-specific cutoff that was lower or equal to the fifth percentile, AT alone was capable of anticipating RDS with a sensitivity and specificity of 78.6% and 89.7% respectively. Furthermore, Khalifa et al stated that RDS was identified in 26.5% of newborns. Infants with RDS had MPA PI and RI values that were considerably greater

than those without (2.51 ± 0.33 and 0.90 ± 0.03 cm/s against 1.96 ± 0.20 and 0.84 ± 0.01 cm/s; respectively, p values of < 0.001).¹⁸ Duncan et al conducted a prospective cohort study to ascertain the prognostic accuracy of the foetal pulmonary artery acceleration time/ejection time for the identification of newborn respiratory complications, and reported that gestational age at delivery was significantly associated with RDS with 85% predictive accuracy for RDS.¹⁹

Additionally, Mohamed et al showed a statistically significant relationship between the occurrence of RDS and exact birth weight, which was considerably lower in those who had the condition.²⁰ RDS progression and infant sex, Apgar at 1 and 5 min, and maternal prenatal dexamethasone treatment all showed statistically significant relationships. When it came to Doppler parameters, there was a statistically significant correlation between the development of RDS and each of the S/D ratios PI and (RI), which were considerably higher in neonates with RDS while those patients had a substantially lower acceleration-time/ejection-time ratio (At/Et) ratio. RDS evolution and PSV have a statistically insignificant relationship. According to Vafaei et al, there was a link between gestational age and the development of RDS.²¹ The infants with RDS have considerably lower pulmonary artery AT ($p < 0.05$). This indicates that compared to foetuses that do not develop RDS, those who do have increased pulmonary vascular resistance and lower pulmonary blood flow. In our research, the examination of the pulmonary artery, the mean pulmonary AT, and the pulmonary AT/ET values all substantially increased with gestational age. The pulmonary artery PI, RI, and ET showed no obvious alterations as gestational age increased.

According to several studies, the rise in the pulmonary artery AT and AT/ET represented the decrease in pulmonary arterial vascular resistance.^{22,23} They also hypothesised that impaired lung maturation was linked to increased muscularization, reduced vascularization, and resistance in the peripheral arteries.

The 5 min Apgar score, and more crucially, a difference in the score from 1 min to 5 min, is a helpful marker of the neonate's responsiveness to resuscitative attempts, according to a follow-up study on 85 newborns with RDS who were under 32 weeks' gestation and weighed under 1500 g.²⁴ The findings demonstrated that the RSD group's Apgar scores at 5 min were considerably lower than those of the control group. Additionally, Chambliss et al observed that neonates with a 5 min Apgar score of 7 had a greater probability of developing RDS.²⁵ They came to the conclusion that in that particular group of patients, the 5-minute score indicating the need for continuing resuscitation may be a sign of lung immaturity or pulmonary disease. Another explanation for the greater likelihood of SNIPPV failure in these individuals is birth hypoxia, which results in diminished central respiratory function and unsuccessful weaning.

Our study has several advantages, such as its prospective observational design, the lack of maternal/fetal comorbidities in the study participants. This increases the possible applications and external validity of this research methods prior to elective delivery of both preterm foetuses, especially in centres without NICUs. Three-dimensional FLV, Doppler, and ultrasonographic evaluations were all completed within 24 hours of delivery, reducing the variability brought on by the lag time between assessment and delivery. All ultrasound readings were completed by a single, qualified sonographer, reducing interobserver and intraobserver mistakes.

Limitations

It was a single-center research with a limited sample size and few instances of newborns with RDS (26) to adequately investigate the association between FLV and RDS, some cases didn't complete the study and were replaced by others, and COVID pandemic that elongated the study time.

CONCLUSION

3D FLV and EFW measurement using ultrasonography provide the benefit of being a non-invasive, accessible, and reliable method that only takes a few minutes to be estimated and may be a reliable non-invasive indicator of the incidence of newborn RDS in preterm pregnancies when the risk of RDS progression is present. FLV is a significant predictor for neonatal RDS at a cutoff for ≤ 35 cm³ with sensitivity 88.5% and specificity 68.4%.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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