A Non-Invasive Window into Fetal Breathing: The Power of Pulmonary Artery Doppler

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Abstract-
Background: This observational prospective cohort study aimed to assess the predictive efficacy of fetal main pulmonary artery (MPA) Doppler indices for the development of neonatal respiratory distress syndrome (RDS) in pregnant women between 28 and 40 weeks of gestation.
Design of Study: The research assessed the diagnostic efficacy of MPA Doppler measures for the diagnosis of newborn RDS, including pulsatility index (PI), resistance index (RI), and acceleration time/ejection time (AT/ET). The predictive power of Doppler data was assessed by contrasting them with clinical results.
Results: Nine (22%) of the forty eligible fetuses experienced neonatal RDS. The development of RDS was found to be significantly correlated with the AT/ET ratio, with the RDS-positive group showing a lower mean AT/ET ratio (0.27) than the RDS-negative group. However, no statistically significant differences were found in PI and RI between the two groups. A cut-off value of 0.3 for AT/ET predicted the development of RDS with a sensitivity of 77.78% and specificity of 83.87%.
Conclusion: The research findings indicate that the development of newborn RDS can be accurately predicted with high sensitivity and specificity by foetal MPA Doppler indices, specifically the AT/ET ratio. These results highlight the MPA Doppler's potential as a useful technique for early detection and treatment of newborns at risk for RDS.

Keywords: **Pulmonary artery, Doppler indices, Neonatal respiratory distress syndrome (RDS), Preterm birth.**

INTRODUCTION:

Respiratory distress syndrome (RDS) poses a grave threat to neonatal health, particularly among premature infants, and remains a critical concern worldwide. RD is reported in roughly 50 % of newborns before 30 weeks of gestation across the world[3]. About 200,000 infants are affected with NRD each year in India[3]. Neonatal death & morbidity are largely attributed to RD[3].

The escalating rate of caesarean sections contributes significantly to the incidence of RDS, leading to heightened fetal mortality and morbidity. Timely assessment of fetal lung maturity assumes paramount importance in reducing RDS incidence.

Traditionally, the determination of fetal lung maturity relied heavily on invasive procedures such as amniocentesis, involving the measurement of various biochemical markers in the amniotic fluid. However, the invasive nature of these methods limits their applicability and underscores the need for alternative, non-invasive approaches.

In response to these challenges, there is a growing imperative to explore non-invasive diagnostic modalities for predicting neonatal RDS. Fetal pulmonary artery Doppler emerges as a promising sonographic technique, offering a safe and efficient means of evaluating fetal lung maturity without the associated risks of invasive procedures. The ability to assess fetal lung maturity noninvasively is crucial for informing decisions regarding pregnancy continuation or termination, thereby optimizing neonatal outcomes.

Utilising ultrasound-based techniques for assessing fetal lung maturity offers a viable solution, leveraging the Doppler effect to characterise maternal-fetal circulation and providing valuable insights into pulmonary vascular dynamics.

In this study, we investigate the utility of fetal pulmonary artery Doppler as a non-invasive tool for predicting neonatal RDS, aiming to enhance prenatal care practices and improve outcomes for premature infants.

MATERIAL AND METHODS:

This is a cross-sectional observation study carried out in the Department of Radio-Diagnosis at Maharajah's Institute of Medical Sciences, Vizianagaram from August 2023 and April 2024. A total of 40 antenatal females were subjects in this study.

Study Design: Cross-sectional observational study
Study Location: This was a tertiary care teaching hospital-based study done in the Department of Radio-diagnosis at Maharajah's Institute of Medical Sciences, Vizianagaram.
Study Duration: August 2023 and April 2024
Sample size: 40
Subjects & selection method: Forty females, aged between 18 and 41 years and with gestational ages ranging from 28 to 40 weeks, were enrolled in this study. They were either admitted for elective caesarean delivery or were attending the delivery unit either in active labour or indicated for elective caesarean section. The study specifically included women with uncomplicated singleton pregnancies. Upon obtaining informed consent from the participants, a thorough medical history was obtained, and ultrasound examinations were performed to assess fetal well-being and pulmonary artery Doppler parameters.
Inclusion criteria
Pregnant women with singleton and gestational age ranging from 28 to 40 weeks, admitted for safe confinement & expected to deliver within 48 hours were included in the study.
Exclusion criteria
Pregnant women with conditions like Preeclampsia, Diabetes mellitus, Foetal chromosomal abnormality, Multiple pregnancies and Intrauterine growth restriction were excluded from the study.

PROCEDURE METHODOLOGY

The prenatal ultrasound assessments were conducted using a Mindray DC-70 Exp ultrasound machine equipped with a 3.5 to 5.0MHz convex transducer, facilitating a detailed examination of fetal anatomy and physiology. Pregnant individuals were positioned supinely during the scans, enabling comprehensive evaluation of fetal biometry parameters including biparietal diameter (BPD), femur length (FL), and head circumference (HC). These measurements were pivotal for estimating gestational age and detecting potential complications such as intrauterine growth restriction (IUGR) or macrosomia. Additionally, assessments of the amniotic fluid index were performed to monitor amniotic fluid levels, providing further insights into fetal well-being.
Visualizing the fetal main pulmonary artery (MPA) was achieved by adjusting the transducer to obtain the three-vessel view, an essential step for assessing fetal cardiovascular health. Doppler waveforms obtained from the MPA exhibited characteristic patterns, aiding in distinguishing them from other vascular structures. Doppler velocity parameters, including acceleration time (AT), ejection time (ET), peak systolic velocity (PSV), end-diastolic maximum velocity (EDV), pulsatility index (PI), and resistance index (RI), were meticulously measured either manually or automatically using dedicated software.
Subsequent to delivery, clinical data were meticulously extracted from medical records, with a particular focus on neonatal outcomes. Respiratory distress syndrome (RDS) diagnosis was based on clinical manifestations such as tachypnea, retractions, and nasal flaring, in conjunction with characteristic chest X-ray findings indicative of pulmonary immaturity. These meticulous assessments, encompassing both prenatal and postnatal stages, ensured a comprehensive evaluation of fetal and neonatal health, allowing for timely interventions when necessary to optimize outcomes.

STATISTICAL ANALYSIS

The data were statistically summarized in terms of mean, standard deviation (SD), and range for parametric quantitative data, while frequencies and percentages were used when appropriate. The comparison of parametric quantitative data between study groups was conducted using the Independent Samples T-test. For non-parametric quantitative data, the Mann-Whitney test was employed. When the expected frequency was less than or equal to 5, the exact test or Fisher's exact test was utilized for qualitative data comparison between the two groups.
Correlation analysis between various variables was performed using Pearson's correlation equation for linear relationships in normally distributed variables and Spearman's rank correlation equation for non-normal or non-linear monotonic relationships.
To evaluate the diagnostic accuracy of Doppler parameters, receiver operating characteristic (ROC) curves were constructed, plotting sensitivity (true-positive rate) against specificity (false-positive rate).
Statistical significance was determined by p-values < 0.05. All statistical analyses were conducted using SPSS software (version 20).

RESULTS

A total of 65 patients were initially examined, but 25 cases were excluded from the study. Exclusions included 14 patients who gave birth more than 48 hours after the ultrasound examination, 8 cases with respiratory distress (RD) due to causes other than Respiratory Distress Syndrome (RDS), 2 cases with missing neonatal data, and one case due

to suboptimal ultrasound data. Consequently, 40 fetuses were eligible for analysis, with 9 diagnosed with RDS (RDS +ve group) and 31 without RDS (RDS -ve group).

Maternal data (Table 1), comparison between the groups revealed no statistically significant differences in maternal age or parity. However, there was a significant difference in mean gestational age between neonates with RDS (31.6 +/- 2.9 weeks) and those without RDS (35.3 +/- 1.5 weeks), with p-value < 0.001.

Regarding neonatal outcomes (Table 2), significant differences were observed between the RDS +ve and RDS -ve groups in terms of gestational age, amniotic fluid index (AFI), neonatal weight and need for NICU admission. The RDS +ve group had lower gestational age (mean 31.6 weeks), AFI (median 7.3), and weight (median 2210.3 grams) compared to the RDS -ve group. All RDS +ve neonates were admitted to the NICU, while only 3 cases (9.7%) from the RDS -ve group required NICU admission. Additionally, fetal gender showed no statistically significant correlation with RDS development.

In the study assessing MPA Doppler indices (Table 3), in fetuses with and without Respiratory Distress Syndrome (RDS), significant correlations were observed, particularly with the AT/ET ratio. The AT/ET ratio was notably lower in the RDS-positive group compared to the RDS-negative group, indicating a potential predictive value for RDS development. Conversely, no significant differences were observed in PI and RI between the two groups.

Specifically, the mean AT/ET ratio in MPA Doppler velocimetry was significantly lower in fetuses that subsequently developed RDS (mean 0.27 ± 0.05) compared to those without RDS (mean 0.34 ± 0.05), with a P-value <0.001. This suggests a positive correlation between the AT/ET ratio and RDS outcome.

Furthermore, using an AT/ET cut-off point of 0.3(Table 4), RDS diagnosis could be achieved with high sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (77.78%, 83.87%, 58.3%, 92.9%, and 82.5% respectively). This cut-off point suggests that a ratio greater than 0.3 may indicate mature fetal lung development.

Table (1): Maternal Data

Maternal Data	**RDS -Ve (N=31)**	**RDS +Ve (N=9)**	**P value**
Age Range **Mean ± SD**	(19-36) 25.8±5.5	(18-40) 27.1±8.4	0.551
Parity **PG** **MG**	 7 (22.6%) 24 (77.4%)	 3 (33.3%) 6 (66.7%)	 0.327
GA(LMP) Range **Mean ± SD**	(31-39) 35.3 ±1.5	(28.7-37.3) 31.6±2.9	<0.001*

Table no 1: Shows the maternal data, including age, parity, and gestational age, with their mean values and p-value, compared between RDS +ve and RDS -ve groups.

Table (2): Fetal and neonatal data

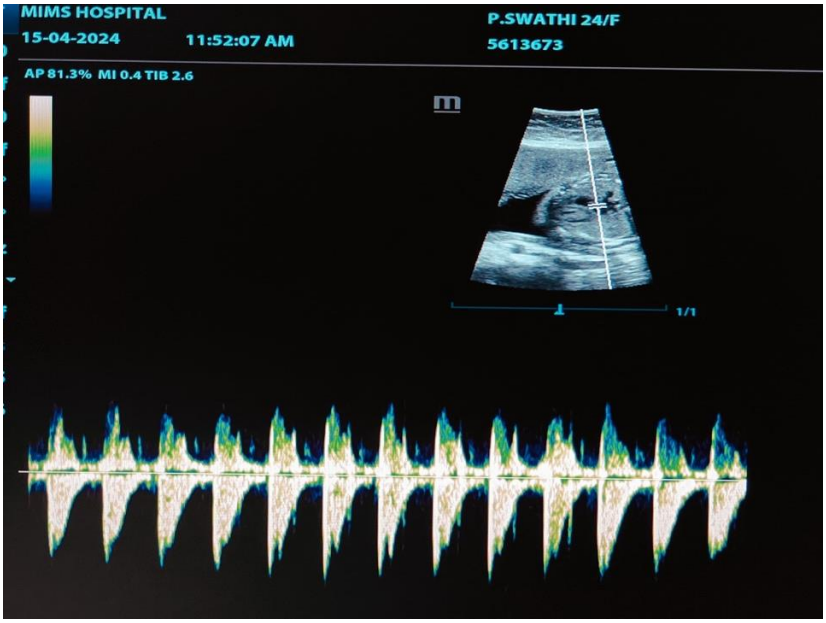
Fetal and Neonatal Data	**RDS -Ve (N=31)**	**RDS +Ve (N=9)**	**P value**
GA (US) Range **Mean ± SD**	30-39 (37.3±1.7)	28.9-39 (32.7±3.3)	<0.001*
AFI Median	12.2	7.3	0.003*
Weight Median	3055.1	2210.3	0.001*
Female	13 (41.9%)	3 (33.3%)	
Male	18 (58.1%)	6 (66.7%)	
NICU Admission **No** **Yes**	 28 (90.3%) 3 (9.7%)	 0 (0%) 9 (100%)	<0.001*

Table no2: Shows fetal data like gestational age, amniotic fluid index, weight, sex and NICU admission with their mean values and p-value, compared between RDS +ve and RDS -ve groups compared between

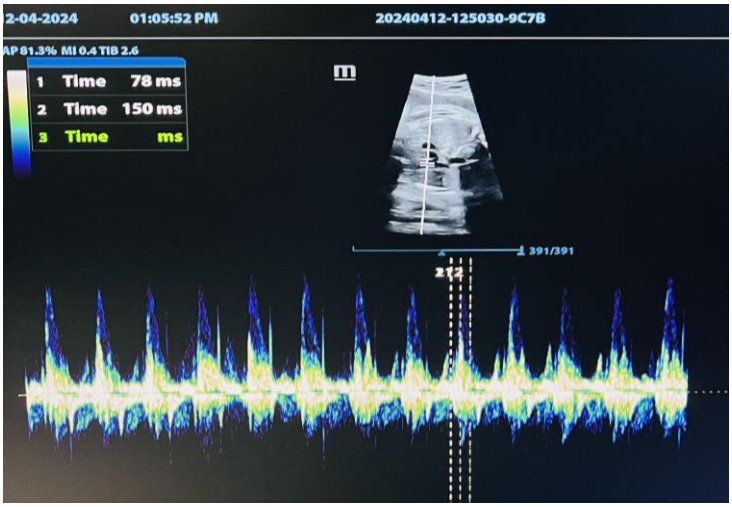
Table (3): MPA Doppler indices

MPA Doppler Indices	RDS -Ve (N=31)	RDS +Ve (N=9)	P value
RI Range **Mean ± SD**	0.55-0.99 0.82±0.11	0.57-0.93 0.77±0.13	0.247
PI Range **Mean ± SD**	1.67-3.54 2.43±0.48	1.5-3.1 2.24±0.56	0.317
AT/ET Range **Mean ± SD**	0.19-0.4 0.34±0.05	0.2-0.35 0.27±0.05	0.001*

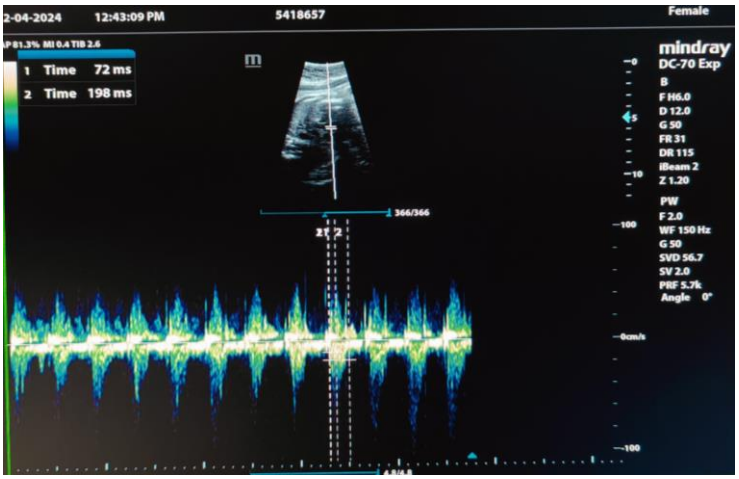
Table no3: Shows the main pulmonary artery Doppler indices compared between RDS +ve and RDS -ve groups.



Main pulmonary artery doppler analysis



AT/ET ratio of MPA doppler



AT/ET ratio of MPA doppler

Table (4): Analysis of AT/ET for prediction of RDS +Ve neonates

Parameter	Value
Optimal cut-off	≤ 0.3
95% CI	0.695-0.939
Sensitivity	77.78%
Specificity	83.87%
PPV	58.3%
NPV	92.9%
Accuracy	82.5%

Table no4: Shows the analysis of Acceleration time by ejection time for the prediction of RDS +ve neonates with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy main pulmonary artery Doppler indices.

DISCUSSION:

Respiratory distress syndrome (RDS) in newborns, also known as hyaline membrane disease, poses a significant threat to premature infants, often leading to neonatal mortality. Accurately assessing fetal lung maturity is crucial for determining the optimal time for pregnancy termination, particularly in high-risk pregnancies. While invasive tests like amniocentesis offer biochemical indicators such as the lecithin/sphingomyelin (L/S) ratio, they carry inherent risks. Hence, non-invasive techniques play a pivotal role in guiding clinical decisions, including delivery planning and administering antenatal steroids to enhance fetal lung maturity and mitigate the risks of preterm birth.

Our analysis of maternal data (Table 1) revealed that maternal age and parity did not influence RDS development. However, gestational age and fetal weight significantly correlated with RDS incidence, aligning with previous findings. Prematurity emerges as the most critical factor in RDS development. While fetal sex did not impact RDS occurrence in our study, the small sample size may have influenced this result. Notably, all RDS-positive neonates were admitted to the NICU, underscoring the severity of the condition.

Despite challenges in obtaining longitudinal sections of the fetal main pulmonary artery, we focused on parameters like the acceleration time to ejection time ratio (AT/ET) and pulsatility index, which are less affected by insonation angle variability. This approach ensures more reliable assessment of fetal pulmonary artery Doppler indices, despite the limitations posed by angle correction.

In our study, we found a notable correlation between the acceleration time to ejection time ratio (AT/ET) and the development of neonatal RDS. The AT/ET was significantly lower in the RDS +ve group (mean 0.27) compared to the RDS -ve group (mean 0.34), with a p-value of 0.001. In contrast, both the pulsatility index (PI) and resistance index (RI) showed no statistically significant differences between the two groups, with p-values of 0.317 and 0.247, respectively.

Using an AT/ET cut-off point of 0.3, we predicted the development of neonatal RDS with high sensitivity, specificity, negative predictive value, and accuracy (77.78%, 83.87%, 92.9%, and 82.5%, respectively).
Our results of AT/ET ratios correlated with that of **Alsheikh et al., Keshuraj et al., Moety et al. & Yadav et al. Khalil et al. & Büke et al.**, while our study did not find any significant difference in PI & RI among neonates with & without RD. Therefore, according to our study it is recommended that a fetus with an AT/ET <0.305 should be delivered in a well-equipped hospital with respiratory support facilities because it is at risk of developing neonatal RD.
While Doppler is readily available on many ultrasound machines and provides immediate results, its interpretation is complex and operator-dependent, requiring substantial experience. Thus, inter-observer variability remains a significant limitation, particularly considering its sensitivity in predicting fetal lung maturity.

CONCLUSION:
Based on our findings, fetal pulmonary artery AT/ET emerges as a valuable predictor for fetal lung maturity (FLM) and consequent neonatal respiratory distress syndrome (RDS), offering high sensitivity and specificity. However, to solidify these conclusions and ensure their clinical applicability, larger prospective studies are warranted. These studies would enable a comprehensive assessment of the sensitivity and specificity of AT/ET ratios in predicting FLM. Moreover, they would provide insights into whether AT/ET ratio can effectively replace invasive procedures like amniocentesis for FLM testing, thereby potentially mitigating the risk of neonatal RDS.

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