*Research Article*

# The role of different fetal pulmonary artery Doppler indices in the prediction of neonatal respiratory distress syndrome

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## Abstract

**Objective:** To study whether fetal main pulmonary artery (MPA) Doppler indices can predict the development of neonatal respiratory distress syndrome (RDS). **Study Design:** This Observational Prospective cohort study included pregnant women between 28- and 40-weeks gestation. The diagnostic accuracy of MPA Doppler measurements (pulsatility index (PI), resistance index (RI) and acceleration time/ejection time (At/Et)) for diagnosis of neonatal RDS was tested by comparing the Doppler findings with the clinical outcome. **Results:** Of the 40 eligible fetuses, 9 (22%) developed neonatal RDS There was a significant correlation between the AT/ET and the development of the RDS as the AT/ET was significantly lower in the RDS +ve group (mean 0.27) in comparison to the RDS -ve group (mean 0.34) (P 0.001). While both PI and RI showed no statistically significant difference in between the two groups. A cutoff value of 0.3 for At/Et predicted the development of RDS (sensitivity: 77.78%, specificity: 83.87%). **Conclusion:** Development of neonatal RDS can be predicted using the MPA At/Et with high sensitivity and specificity.

**Keywords:** pulmonary artery, Doppler indices, neonatal respiratory

## Introduction

Respiratory distress syndrome (RDS) of the newborn is the most serious cause of respiratory distress in premature infants [1]. This represents an imperative issue in our country as 7.3% of all live births in Egypt are premature [2]. The steady increase in the number of cesarean sections in our hospitals remains a major contributing factor to this issue, leading to an increase in fetal mortality and morbidity[2].

Proper evaluation of fetal lung maturity is of utmost importance for determining the optimal time for pregnancy termination to help decrease the incidence of RDS. However, all the available biochemical tests for lung maturity evaluation require amniocentesis which is an invasive procedure that carries major , although low in incidence, risks including preterm premature rupture of membranes, preterm labor, placental abruption, fetomaternal hemorrhage, fetal injury, and rarely fetal or even maternal death [3].

This prompted us to investigate a noninvasive sonographic technique, fetal pulmonary artery Doppler, to evaluate its value in the prediction of neonatal RDS.

## Patients and Methods

### Participants

This Observational Prospective cohort study was conducted at Minia Maternity and Children University Hospital, Minia, Egypt (From May 2018 to December 2018) and was approved by the hospital research ethics committee.

Our study included 40 patients chosen from among cases delivering in Minia Maternity & Children University Hospital with the following inclusion and exclusion criteria

### Inclusion criteria

1- Gestational age between 28-40 w.
2- Ultrasonography done within 48 hours of delivery.
3- Singleton pregnancy.

### Exclusion Criteria:

1- Pregnant females less than 28 weeks of gestational age or more than 40 weeks.
2- Multiple gestations.
3- Uncertain gestational age.
4- Corticosteroid administration between ultrasound examination and delivery.
5- Congenitally malformed fetus.

**Sonographic antepartum assessment of each case**

All sonographic examinations were done by one examiner (Mohamed Kamaleldin Abdelhamid) using an Aplio™ 500 ultrasound machine (Toshiba Medical Systems Co. Ltd, Tamara, Japan) equipped with a 3.5to 5.0MHz convex transducer.

Pregnant women were scanned in the supine position. Routine prenatal sonographic examination including fetal biometry ( BPD , FL and HC) which were used to estimate the fetal gestational age and the expected fetal weight and to rule out IUGR or macrosomia. Amniotic fluid index was measured as well.

The fetal main pulmonary artery (MPA) was visualized by slightly translating the transducer superiorly from the four chamber cardiac view to obtain the three vessel view (3VV) (Figure 1). The pulsed Doppler sample gate is placed at the middle of the fetal MPA (between the pulmonary valves and the pulmonary artery bifurcation). After enlarging the image as much as possible, the sample gate was adjusted to 3 mm.

Fetal MPA Doppler waveforms produce a specific "spike and dome" pattern, and a small notch at the end of systole (figure 2). This specific shape of MPA waveform is important to differentiate it from ductus arteriosus waveform which is rounded, full and triangular shaped.

After the optimal fetal MPA waveform were obtained, relevant Doppler velocity variables were measured three times using manual trace, and measurements are averaged. The Doppler variables include acceleration time (AT; the time interval from the foot to the top of PSV), ejection time (ET; from the beginning to the end of ventricular systole), From these measurements, the AT/ET ratio was calculated (figure3).

Other Doppler parameters were measured using automatic trace such as the maximum blood flow velocity reached during systole (PSV), end-diastolic maximum velocity (EDV), pulsatility index(PI), and resistance index(RI)

**Diagnosis of neonatal RDS**

Upon delivery, the route of delivery was recorded as well as the neonatal sex. A pediatrician who was blinded to the fetal MPA Doppler measurements, handled the neonate. Neonatal birth weight (NBW) and Apgar score (at 1 and 5min) were recorded. The diagnosis of RDS was based on clinical signs of respiratory distress (tachypnea, retractions and/or nasal flaring), supplemental oxygen requirement of 0.4 or greater for at least 24h and typical chest X-ray findings with reticulogranular patterns, air bronchograms and ground glass appearance

**Statistical analysis**

Data were statistically described in terms of mean, SD., and range or frequencies and percentages when appropriate. Comparison of parametric quantitative data between the study groups was carried out using Independent samples T test. For comparing Non-parametric quantitative data, Mann Whitney test test was performed. Exact test was used instead when the expected frequency is o5 Fisher exact test for qualitative data between the two groups

Correlation between various variables was carried out using Pearson's correlation equation for linear relation in normally distributed variables and Spearman's rank correlation equation for non-normal variables/nonlinear monotonic relation. The diagnostic accuracy of Doppler parameters was assessed using receiver operating characteristic (ROC) curve, which plot the sensitivity (true-positive rate) to the specificity (false-positive rate)

P-values < 0.05 was considered statistically significant. All statistical calculations were processed on an IBM-PC compatible computer using SPSS (version 20)
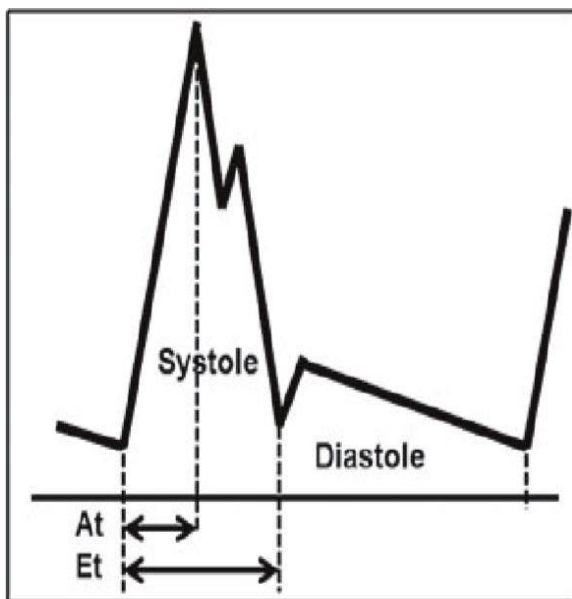
**Figure 1 The three vessels view**



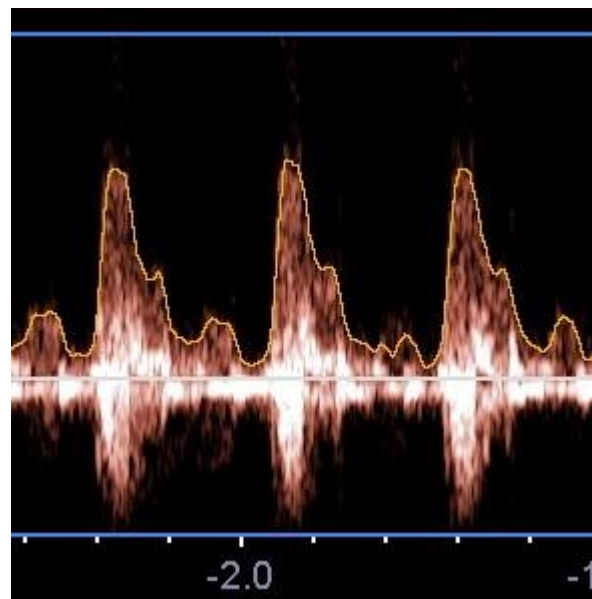**Figure (3): Acceleration and ejection time[139]**



**Figure (2): Spike and Dome Pattern**

## Results

A total of (65) patients were examined. Twenty-five cases were excluded from the study: 14 patients gave birth more than 48 hours after the ultrasound examination, 8 cases had RD due to causes other than RDS, 2 cases were discarded for missed neonatal data and one case for suboptimal ultrasound data. Finally, (40) fetuses were eligible for analysis, among which 9 were diagnosed as RDS (+ve) (RDS +ve group) and 31 were RDS (-ve) (RDS -ve group).

**Table (**1 shows the maternal data of our study groups in terms of maternal age, parity and gestational age. The gestational age of the study groups ranged from 28 to 39 weeks. all of them were admitted to our hospital and delivered within 48 hours after our ultrasound exami-nation. There were no statistically significant differences between the neonates with RDS and those without RDS in terms of maternal age and parity However, the mean gestational age was

32.7+/- 2.9 weeks. in those neonates who

developed RDS (RDS +ve group), compared to 37.6+/- 1.5 weeks. in those neonates who did not develop RDS (RDS -ve group). The difference between the two group was statistically significant (P value <0.001)

According to table 2 there was statistically significant differences between the two groups in terms of gestational age, amniotic fluid index, neonatal weight, 5min APGAR score and the need for NICU admission The RDS +ve group had significantly lower gestational age, measured by ultrasound, (mean 32.7 w), AFI (median 7.6) and weight (median 2159.6 gm) in comparison to the RDS –ve group. All RDS +ve neonates were admitted to NICU (100%) while in the RDS -ve group just 3 cases (9.7%) were admitted to NICU. 5 minutes Apgar score was significantly lower in neonate who subsequently developed RDS. Fetal gender and 1 min APGAR score showed no statistically significant relation.

Table 3 shows MPA Doppler indices in fetuses with or without RDS. Correlating the Doppler indices of the main fetal pulmonary artery,

namely pulsatility index(PI), resistance index (RI), and the acceleration-time/ejection-time ratio (At/Et) and their role in predicting respiratory distress syndrome(RDS) There was a significant correlation between the AT/ET and the development of the RDS as the AT/ET was significantly lower in the RDS +ve group (mean 0.27) in comparison to the RDS -ve group (mean 0.34). While both PI and RI showed no statistically significant difference in between the two groups.

According to tables 3,4 and figure 4 AT/ ET mean in MPA Doppler velocimetry was significantly lower in fetuses which subsequently developed RDS (0.27 +/- 0.05) than those without RDS (0.34 +/- 0.05), (P-Value <0.001). It means that At / Et ratio was positively correlated with RDS outcome. Considering AT/ET cutoff point as 0.3, RDS can be diagnosed with high sensitivity, speci-ficity, positive predictive value, negative predictive value and accuracy (77.78%, 83.87%, 58.3%, 92.9% and 82.5% respec-tively). It means that ratio > 0.3 demonstrates mature fetal lung. The area under curve was 0.844.

**Table (1): Maternal Data**

|  |  | RDS -Ve | RDS +Ve | P value |
|---|---|---|---|---|
|  |  | N=31 | N=9 |  |
| **Age** | *Range* | (19-38) | (17-42) | *0.551* |
|  | *Mean ± SD* | 26.1±5.5 | 27.9±8.4 |  |
| **Parity** | *PG* | 7(22.6%) | 3(33.3%) | *0.327* |
|  | *MG* | 24(77.4%) | 6(66.7%) |  |
| **GA (LMP)** | *Range* | (31-39) | (28.7-37.3) | *<0.001\** |
|  | *Mean ± SD* | 37.6±1.5 | 32.7±2.9 |  |

- *Independent samples T test for parametric quantitative data between the two groups*
- *Mann Whitney test for Non-parametric quantitative data between the two groups*
- *Fisher exact test for qualitative data between the two groups*
- *\*: Significant difference at P value < 0.05*

**Table (2): Fetal and neonatal data**

| | | RDS -Ve | RDS +Ve | P value |
|---|---|---|---|---|
| | | N=31 | N=9 | |
| GA (US) | *Range* *Mean ± SD* | (30-39) 37.3±1.7 | (28.9-39) 32.7±3.3 | *<0.001\** |
| AFI | *Median* *IQR* | 11.7 (10-13) | 7.6 (4-11) | *0.003\** |
| Weight | *Median* *IQR* | 3068.5 (3050-3210) | 2159.6 (1364-2315 | *0.001\** |
| Sex | *Female* *Male* | 13(41.9%) 18(58.1%) | 3(33.3%) 6(66.7%) | *0.717* |
| APGAR 1m (less than7) | *No* *Yes* | 31(100%) 0(0%) | 8(88.9%) 1(11.1%) | *0.225* |
| APGAR 5m (less than 7) | *No* *Yes* | 31(100%) 0(0%) | 6(66.7%) 3(33.3%) | *0.009\** |
| NICU Admission | *No* *Yes* | 28(90.3%) 3(9.7%) | 0(0%) 9(100%) | *<0.001\** |

- *Independent samples T test for parametric quantitative data between the two groups*
- *Mann Whitney test for Non-parametric quantitative data between the two groups*
- *Fisher exact test for qualitative data between the two groups*
- *\*: Significant difference at P value < 0.05*

**Table (3): MPA Doppler indices**

| | | RDS -Ve | RDS +Ve | P value |
|---|---|---|---|---|
| | | N=31 | N=9 | |
| 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\** |

- *Independent samples T test for parametric quantitative data between the two groups*
- *\*: Significant difference at P value < 0.05*

**Table 4 ROC curve analysis of AT/ET for prediction of RDS +Ve neonates**

| | AT/ET |
|---|---|
| **Optimal cutoff** | *≤ 0.3* |
| **AUC** | 0.844 |
| **95% CI** | 0.695-0.939 |
| **P value** | **<0.001\*** |
| **Sensitivity** | 77.78% |
| **Specificity** | 83.87% |
| **PPV** | 58.3% |
| **NPV** | 92.9% |
| **Accuracy** | 82.5%% |

- *AUC: Area Under Curve           - CI: Confidence Interval*
- *PPV: Positive predictive value    - NPV: Negative Predictive value*
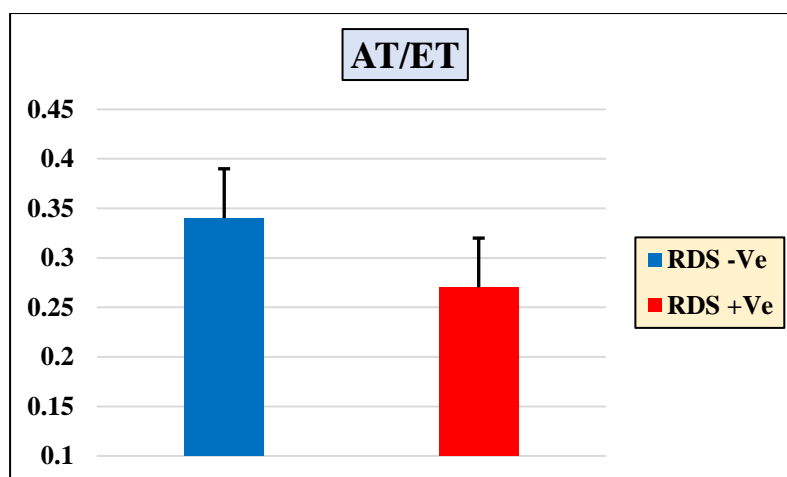- *\*: Significant level at P value < 0.05*

**Figure 4 AT/ET in the two groups**

## Discussion

Respiratory distress syndrome (RDS) of the newborn, also called hyaline membrane disease, is one of the serious causes of respiratory distress in premature infants, correlating with structural and functional lung immaturity and it is one of the commonest causes of neonatal mortality [4]. . Detecting those fetuses at risk of RDS by accurate evaluation of fetal lung maturity is of utmost importance for determining the optimal time for pregnancy termination, especially in high risk pregnancies.

A number of biochemical tests have been developed to predict the risk of RDS. These tests, such as, the lecithin/sphingomyelin (L/S) ratio require amniocentesis. However, amniocentesis is an invasive procedure and is associated with a small but real risk to the pregnancy, including preterm premature rupture of membranes, preterm labor, placental abruption, fetomaternal hemorrhage, fetal injury, and rarely fetal or even maternal death [3].

One of the values of using noninvasive techniques is guiding the clinical decisions concerning delivery planning and administering antenatal steroids. The clinician has to balance the benefits of a preterm birth on both mother and child against the obvious risks of preterm births for the neonate. Another theoretical possible way of using a high-risk result would be to use as an indication for antenatal steroids, to enhance fetal lung maturity and to estimate the deleterious effects of the antenatal steroids given.

Analysis of maternal data results (table 1) showed that both maternal age and parity did not affect the development of RDS. Our study showed that both gestational age and fetal weight were significantly correlated with development of neonatal RDS as both were lower on those who eventually developed neonatal RDS (P value < 0.001). This is in agreement with the previous reports[5-9], making gestational age and hence prematurity the most important factor in neonatal RDS development.

Our results showed that fetal sex did not affect the occurrence of RDS, this is in contrast to the known male disadvantage in respiratory morbidity[10]. However, this can be attributed to the low number of cases included in our study.

All RDS +ve neonate were admitted to NICU (100 %), while only 3 cases (9 .7percent) in the RDS –ve group were admitted to NICU. This is expected as all who developed RDS were assumed to be admitted to NICU.

In our study, we found it is rather difficult to obtain a longitudinal section in the fetal main pulmonary artery. Therefore, an accurate correction of the insonation angle could not be achieved; thus, we did not include pulmonary artery velocimetry parameters (PSV, EDV) in our results. This also may explain the wide variability of those parameters in previous studies of the fetal pulmonary artery Doppler[5-7].

We resorted to parameters that were not significantly affected by the angle of insonation; such as, acceleration time to ejection time ratio (AT/ET), pulsatility index

                    **The role of different fetal pulmonary artery Doppler indices in the prediction**

(PI) and resistance index (RI). There was a significant correlation between the AT/ET and the development of the RDS as the AT/ET was significantly lower in the RDS +ve group (mean 0.27) in comparison to the RDS -ve group (mean 0.34), (P value 0.001). While both PI and RI showed no statistically significant difference in between the two groups, P values 0.317 and 0.247 respectively.

An AT/ ET cut of point of 0.3 predicted the development of neonatal RDS with a high sensitivity, specificity, negative predictive value and accuracy (77.78%,83.87%, 92.9% and 82.5 % respectively).

Our results were in agreement with a study done earlier in the Obstetrics and Gynecology department in our hospital regarding the significant correlation between the AT/ET and the development of RDS. However, in contrast to our results, they also found a significant correlation between the RI and RDS development. This may be due to the different gestational age groups included in both studies[11].

Our results were also in agreement with Guan et al.,[12], Moety et al.,[6], Khanipouyani et al.,[13] and Büke  et al.,[14]. All of them had similar study designs (comparing the fetal main pulmonary artery Doppler with clinical outcome) and also to Schenone et al.,[9]. who compared the AT/ET to albumin/surfactant ratio results.

This significant positive correlation between the AT/ET and fetal lung maturity may be explained as the  elevated AT/ET represents a decrease in fetal pulmonary arterial pressure which is expected in a mature fetal lung.[15]

However , our results contradicted Kim et al.,[5] and Mohamed et al.,[16] who found that Pulmonary artery At/Et ratio was  inversely correlated to fetal lung maturity. The discordance may be due to a variation in study population or details of the ultrasound measurements and equipment.

Doppler is readily available on many ultrasound machines and the results can be obtained immediately. However, it is a rather difficult technique, heavily operator dependent and requires a great deal of experience. Therefore,

there is a great deal of inter-observer variability which is a major drawback for such a sensitive and crucial test.

## Conclusion
We concluded from our study that fetal pulmonary artery AT/ET is valuable in predicting fetal lung maturity and hence development of neonatal RDS with high sensitivity and specificity.

Larger prospective studies are needed to assess the sensitivity and specificity for At/Et ratios to predict FLM and to further assess whether the At/Et ratio can replace amniocentesis for FLM testing with a view to preventing neonatal RDS.

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