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Validity of foetal Doppler indices in predicting postnatal respiratory distress syndrome: a prospective study

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Abstract

Background: Respiratory distress syndrome (RDS) is a potentially fatal condition of neonate occurring due to alveolar surfactant deficiency causing inefficient gaseous exchange and leading to hampered respiratory function. Purpose of our study is to investigate the role of Doppler indices in antenatal prediction of clinical Respiratory Distress Syndrome (RDS) in late preterm and early term foetuses using Main pulmonary artery (MPA) Doppler indices. The current study was conducted on 342 pregnant women between 34 and 39 weeks of gestational age, who came for routine third trimester ultrasound examination. The standard foetal biometric parameters, gestational age and estimated foetal weight were first obtained. The MPA Doppler indices like pulsatility index (PI), resistivity index (RI), peak systolic velocity (PSV), systolic/diastolic ratio and acceleration time/ejection time (At/Et) were recorded and correlated with the postnatal development of RDS.

Results: Of the 342 foetuses, neonatal RDS was diagnosed in 47 foetuses. Foetuses diagnosed with RDS had statistically higher PI and RI values, whereas At/Et ratio and PSV were lower. At/Et ratio, PI and RI, PSV showed significant correlation with gestational age and the most statistically significant correlation was found with At/Et ratio. A cut-off value of 0.2865 (sensitivity 89.45%, specificity 94.79%) and 0.3155 (sensitivity 93.22%, specificity 96.78%) correlated strongly with development of RDS in late preterm foetuses and early term infants.

Conclusion: Foetal MPA indices like PSV, RI, PI and especially Foetal At/Et ratio is a promising non-invasive tool which helps in identifying foetuses at risk and may be very useful to plan delivery in complicated pregnancies and also for better post-natal care of the neonate.

Keywords: Respiratory distress syndrome, Foetal lung maturity, Colour Doppler indices, Acceleration time/ejection time (At/Et ratio)

Background

Respiratory distress syndrome (RDS) is a frequent and morbid condition of the neonate which develops due to deficiency of surfactant in the lung alveoli. This in turn leads to inefficient gaseous exchange leading to hampered respiratory function [1].

Various studies worldwide cite about 50% incidence of RDS in infants born before 30 weeks of gestation [2] and such incidence reduces with increase in gestational age, from about 60–80% in foetuses born at 26–28 weeks, to about 15–30% of those born at 32–36 weeks [3].

Incidence of RDS is higher in India which approximates to about 200,000 infants per year [4]. The mortality rate of infants from RDS remains as high as 40–60% [5, 6]. RDS is a major cause of neonatal mortality and morbidity. Prenatal determination of foetal lung maturity (FLM) is of paramount importance in diagnosing RDS.

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Evaluation of FLM is one of the most challenging processes because we are yet to develop an optimal strategy that can determine it. Several prenatal markers like Lecithin/Sphingomyelin ratio, detection of Phosphatidyl Glycerol, Fluorescence Polarization test and Amniotic Fluid Lamellar body count test are used to analyse FLM. All of these though lucrative, depend on Amniocentesis which in addition to being invasive has a complication rate of approximately 0.7%; some of the worrying complications include preterm rupture of membranes, preterm labour, placental abruption and foeto-maternal haemorrhage [7]. Also, various studies about these methods were not able to confirm the superiority of one test over another [8]. In contrast, USG is a non-invasive, safe, widely available and universally accepted method to evaluate FLM.

In the present study, we have made an attempt to predict the development of neonatal RDS in late preterm and early term infants using MPA colour Doppler indices with special emphasis to At/Et ratio, and to provide a reliable cut-off point for At/Et ratio with high sensitivity and specificity.

Methods

Study design and population

A hospital-based prospective study was conducted for a period of one year (November 2020–2021) in a tertiary level Maternal and child care hospital of South India.

In our Institute, in addition to the routine third trimester ultrasound scan performed between 28 and 32 weeks, we also perform another routine third trimester scan between 34 and 39 weeks of gestation as an Institutional protocol. The inclusion criteria set in the study were all singleton pregnancies with gestational age (measured from dating by certain last menstrual period or by first-trimester USG) between 34 and 39 weeks and only foetuses delivered within 48 h of admission. Exclusion criteria in the study were patients with oligohydramnios (defined as Amniotic Fluid Index (AFI) less than 5 cm), polyhydramnios (defined as AFI more than 25 cm), maternal Gestational diabetes mellitus (GDM), Pregnancy-induced hypertension (PIH), maternal systemic corticosteroid exposure prior to scan, foetal Intra-Uterine Growth Restriction (IUGR), foetuses with structural abnormalities on USG or after delivery and foetuses delivered 48 h after USG. We evaluated a total of 729 pregnant women between 34 and 39 weeks of gestational age. We excluded 57 patients with oligohydramnios, 23 patients with polyhydramnios, 41 patients with GDM, 29 patients with PIH, 39 patients who had received corticosteroids prior to the scan, 54 foetuses with IUGR, 69 foetuses delivered more than 48 h after the USG, 45 foetuses with structural abnormalities on USG and 15 neonates

with structural abnormalities diagnosed only after delivery leaving 357 foetuses. In 15 of those 357 foetuses, the MPA Doppler waveforms could not be elucidated accurately because either the foetal spine was directed anteriorly (8 foetuses) or the women were obese (7 women). Technically acceptable Doppler waveforms were obtained in the rest thus leaving 342 eligible foetuses for final analysis.

Late preterm, in our study, was defined as those infants delivered between 34 0/7 and 36 6/7 weeks of gestation and those delivered between 37 0/7 and 38 6/7 weeks of gestation were defined as early term neonates [9].

Ethical consent

The study was approved by the Institutional ethics review committee. All the participants were informed about the procedure and written and informed consent was obtained.

Imaging techniques

Ultrasound examinations were performed using SAMSUNG RS 80 EVO Ultrasound machine equipped with a 2–6 MHz (Mega Hertz) curvi-linear transducer. All the Doppler examinations were performed by a single Radiologist with 10 years of experience in the field of Obstetric Ultrasonography.

After a routine Antenatal third trimester USG, which included foetal biometry, Estimated Foetal Weight (EFW) and AFI, examination of the foetal heart was done systematically using the three-vessel view, 4 chamber view and outflow tracts. The foetal thorax was carefully analysed in axial view with the foetus at rest, the foetal MPA was followed till the middle of the pulmonary valve and its branching into right and left pulmonary arteries (Fig. 1A and B). The pulsed Doppler technical adjustments like keeping sample gate to about 3 mm and angle of insonation less than 60° were made. Doppler gain and scale were adjusted till Peak Systolic Velocity (PSV) and early diastolic notch were visualized optimally. The MPA Doppler waveform shape is commonly termed as 'Spike and Dome' pattern due to needle-like appearance caused by sharp systolic peak and it also produces a small notch of reversed flow at the end of systole. This waveform is distinctive and must not be confused with a rounded and triangular shaped pattern with greater diastolic flow of ductus arteriosus waveform [10].

After obtaining the optimal MPA waveform, Doppler velocity variables were manually measured thrice and its mean was calculated. At/Et ratio, RI, S/D ratio, PI and PSV were the variables taken into account (Fig. 1C and D). The At /Et ratio was obtained by dividing the time interval from the commencement of ventricular systole till attainment of peak velocity(At) by the time interval

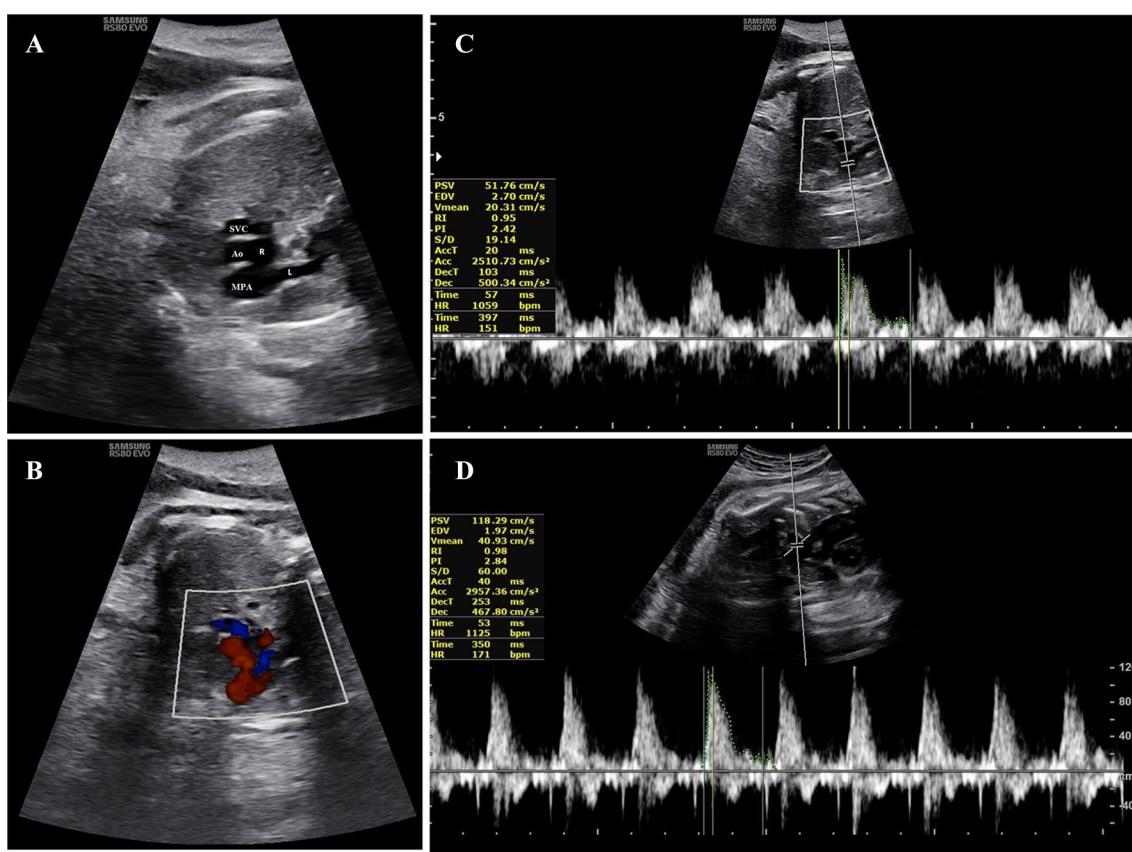


Fig. 1 Evaluation of the foetal main pulmonary artery (MPA) and measurement of Doppler indices. **A** sonographic short-axis view of normal foetal heart at 35 weeks and 3 days of gestational age. Right (R) and left (L) pulmonary arteries are shown branching from the Main pulmonary artery (MPA). Anteriorly and to the right of MPA are aorta and SVC. **B** Colour Doppler image in short-axis view of normal foetal heart at 35 weeks and 3 days of gestational age. **C** Foetal Main pulmonary artery velocity waveforms with measurement of Doppler indices in a foetus at 35 weeks and 6 days of gestational age. On post-natal follow-up, the neonate did not develop RDS. **D** Foetal Main pulmonary artery velocity waveforms with measurement of Doppler indices in a foetus at 35 weeks and 3 days of gestational age which subsequently developed RDS

between the commencement till the end of ventricular systole (Et).

Diagnosis of neonatal RDS

A single paediatrician, who had no knowledge of the foetal MPA Doppler measurements handled the recording of the Neonatal birth weight (NBW) and Apgar scores at 1 min and 5 min. The mode of delivery as well as the neonatal gender was documented.

The diagnosis of RDS was made if any two of the three following criteria were met:

- (1) Respiratory failure (tachypnoea, retraction and/or nasal flaring) shortly after birth and increased oxygen requirement (fractional concentration of inspired oxygen >0.4) for more than 24 h.
- (2) Radiographic findings of respiratory distress syndrome, such as bilateral diffuse ground glass opacity

with air bronchogram in the absence of other respiratory ailments.

- (3) Response to exogenous pulmonary surfactant.

Statistical analysis

Student's T Test was done for comparing independent samples and Chi Square test (χ^2) for comparing categorical data. Pearson's moment correlation equation was used to correlate between different variables. Receiver Operator Characteristic (ROC) analysis was used to predict neonatal RDS after deriving optimum cut-off value of At/Et ratio.

p values of <0.05 was considered statistically significant. The collected data were entered in Microsoft Excel and analysed using SPSS version 24.0.

Table 1 General comparison of various characteristics in foetuses with and without neonatal RDS

N=342	Foetuses belonging to	Foetuses belonging to	p value
	RDS (+) group	RDS (-) group	
	N=47	N=295	
Maternal age (years)	25.45±4.52	27.51±5.14	0.398
GA at delivery(weeks)	35.23±1.51	36.27±1.64	<0.05
<i>Mode of delivery</i>			
Vaginal (number of)	26 (55.3%)	168 (56.9%)	0.567
C-section(number of)	21(44.6%)	127 (43%)	0.557
<i>Ultrasound measurements:</i>			
AFI (cm)	9.46±2.19	14.21±5.41	<0.05
EFW (g)	2408.08±437.65	2871.83±423.57	<0.05
<i>NEONATAL DATA:</i>			
Male sex	30 (63.8%)	144 (48.8%)	0.03
NBW (g)	2302±405.95	2902±463.67	<0.05
NICU admission	47(100%)	98(33.2%)	<0.05
Apgar 1 min	4.02±0.87	7.27±0.55	<0.05
Apgar 5 min	5.87±0.61	9.45±0.62	<0.05

Results

Of the 342 foetuses that were eligible for final analysis using previously mentioned diagnostic criteria, 47 neonates were diagnosed with RDS. After evaluation for the existence of RDS, they were grouped as RDS (+) positive and RDS (-) negative. Table 1 summarizes maternal and neonatal characteristics of the study population and demographic, clinical and USG findings of both groups were compared. Mean maternal age of RDS (+) group was 25.45±4.52 years and of RDS (-) was 27.51±5.14 years. Mean gestational age of RDS (+) group was 35.23±1.41 weeks and of RDS (-) group was 36.27±1.54 weeks.

The neonates in RDS (+) group were found to be the ones born earlier with lesser gestational age and had lower EFW on USG, lower neonatal birth weight and lower AFI. Significantly lower Apgar score was noted in foetuses with RDS. Male babies were found to have a higher occurrence of RDS. Neonatal Intensive Care Unit (NICU) admission rates also showed clear pattern of differentiation with 100% admission needed for RDS (+) babies, whereas only 33.2% admission for RDS (-) babies. The causes for higher admission were found to be perinatal asphyxia ($n=53$), neonatal hyperbilirubinemia ($n=31$), hypoglycaemia ($n=7$), meconium aspiration ($n=5$) and neonatal convulsion ($n=2$).

The mean MPA At/Et ratio was significantly less in foetuses diagnosed with RDS compared to RDS (-) group (0.2865 ± 0.039 vs. 0.3357 ± 0.058 , $p<0.05$ in late preterm and 0.3155 ± 0.044 vs. 0.3527 ± 0.056 , $p<0.05$ in early term infants).

Mean MPA PI values when compared statistically were found to be higher in foetuses belonging to RDS (+) group (2.67 ± 0.14 vs. 2.32 ± 0.16 , $p<0.05$ in late preterm and 2.55 ± 0.11 vs. 2.02 ± 0.19 , $p<0.05$ in early term infants). Mean MPA RI values when compared statistically were found to be higher in foetuses belonging to RDS (+) group (0.92 ± 0.16 vs. 0.83 ± 0.08 , $p<0.05$ in late preterm and 0.81 ± 0.02 vs. 0.75 ± 0.07 , $p<0.05$ in early term infants).

Whereas PSV was distinctively lower in foetuses with RDS compared with RDS (-) group (64.93 ± 1.88 vs. 68.19 ± 0.06 cm s $^{-1}$; $p<0.05$ in late preterm and 73.37 ± 0.56 vs. 76.44 ± 0.12 cm s $^{-1}$; $p<0.05$ in early term infants). S/D ratio showed no significant difference of results between the two groups. (Table 2A and B).

In an attempt to predict the occurrence of RDS in at risk foetuses using Doppler indices a ROC curve was constructed and optimal cut-off value of At/Et ratio was determined (Area Under Curve=0.883, 95% [CI 0.810 to 0.956; $p<0.05$ in late preterm] and Area Under Curve=0.926, 95% [CI 0.854 to 0.998; $p<0.05$ in early term infants]). The specificity and sensitivity were found to be highest at 94.79% and 89.45% when the cut-off value was optimized at 0.2865 in late preterm infants. Similarly, in early term infants, the cut off value of At/Et ratio was 0.3155 with specificity of 96.78% and a sensitivity of 93.22% (Table 3). ROC curve analysed is depicted in Fig. 2A and B.

Spearman's correlation co-efficient indicated that there was significant ($p<0.05$) correlation between GA and At/Et ($r=0.229$), PSV ($r=0.473$), PI ($r=-0.317$) and RI

Table 2 Comparison between MPA Doppler indices in foetuses with and without neonatal RDS

RDS	Mean	Std. Deviation	Std. Error Mean
A. 34 0/7–36 6/7 weeks of gestation			
At/Et	Yes	0.2865	0.03978
	No	0.3357	0.05849
PSV	Yes	64.93	1.88540
	No	68.19	0.06126
PI	Yes	2.67	0.14265
	No	2.32	0.16640
RI	Yes	0.92	0.16839
	No	0.83	0.08695
S/D	Yes	6.88	0.41068
	No	6.86	0.33922
B. 37 0/7–38 6/7 weeks of gestation			
At/Et	Yes	0.3155	0.04410
	No	0.3527	0.05606
PSV	Yes	73.37	0.56097
	No	76.44	0.12432
PI	Yes	2.55	0.10468
	No	2.02	0.19822
RI	Yes	0.81	0.02630
	No	0.75	0.07112
S/D	Yes	6.92	0.49990
	No	6.95	0.31999

Table 3 Statistical parameters related to At/Et ratio predicting occurrence of RDS

	Cut off value	Sensitivity (%)	Specificity (%)	Area under the curve
At/Et ratio (34 0/7–36 6/7 weeks of gestation)	0.2865	89.45	94.79	0.883
At/Et ratio (37 0/7–38 6/7 weeks of gestation.)	0.3155	93.22	96.78	0.926

($r = -0.313$), of which the correlation was found to be strongest with At/Et ratio. (Table 4).

Discussion

As maturation of lung occurs with increasing gestational age, the pulmonary vasculature also develops with increase in number of pulmonary arteries, whereas there is a slight decrease in pulmonary arterial vascular resistance [11, 12]. With the support of these facts

the diagnostic accuracy of foetal MPA Doppler indices in predicting the occurrence of neonatal RDS in late preterm and early term foetuses was examined in our study. This gestational age (34 to 39 weeks) was appropriately chosen because the foetal lung is immature before 34 weeks thus rendering the testing of FLM useless before 34 weeks. Development of RDS was found to be lowest when the foetuses were delivered after 39 weeks of gestation, so many studies suggested that Caesarean section should be carefully planned around this gestational age [13, 14]. Thus, between 34 and 39 weeks of gestation is an optimal timeline for the possibility of early detection of developing RDS and was selected in our study. Hence, it is also appropriate for an obstetric surgeon to test for foetal lung maturity before considering to deliver a foetus in this particular gestational age range.

The results of our study showed that foetuses which developed RDS exhibited a significantly lower At/Et ratio and reduced PSV compared to foetuses that did not develop RDS. PI and RI values were elevated in the former. This indicated that foetuses that developed RDS had pulmonary vascular resistance and pressure which was higher and lower pulmonary blood flow in comparison to those without RDS. Our results correlated well with the study done by Guan et al. [15] where MPA At/Et ratio was significantly lower in preterm foetuses diagnosed with RDS. ET, EDV, PI, and RI showed no correlation with neonatal RDS in their study which is in contrast to our study. Moreover, their study included preterm foetuses only. Our study revealed that MPA At/Et ratio and PSV values increase directly, whereas PI and RI values decrease with gestational age of which At/Et ratio correlated strongly with gestational age. There was no significant change in the S/D ratio throughout gestation. Our results were in total agreement with the study done by Moety et al. [16] and Chaoui et al. [17]. The authors of the latter inferred that there was a rise in pulmonary vascular compliance and fall in mean pulmonary artery pressure with the advancement of pregnancy, leading to a gradual increase in pulmonary blood flow. However, their study was done in foetuses at high-risk for lung-hypoplasia. Rasanen et al. [18] inferred that there is an inverse relationship between gestational age and RI which is caused by the increase in diameter of the vascular lumen, increased vascular elasticity of pulmonary vessels along with continuing pulmonary angiogenesis. [19] This is also a suitable explanation for the findings in our study that RI decreases with advancing gestational age. Laban et al. [20] identified mean foetal lung volume (cut-off $\geq 32 \text{ cm}^3$) and pulmonary artery (PA)-RI (cut-off ≤ 0.74) as reliable predictors of neonatal RDS. They inferred that combination of these two measures had a greater predictive value than when either measure used alone. The sensitivity

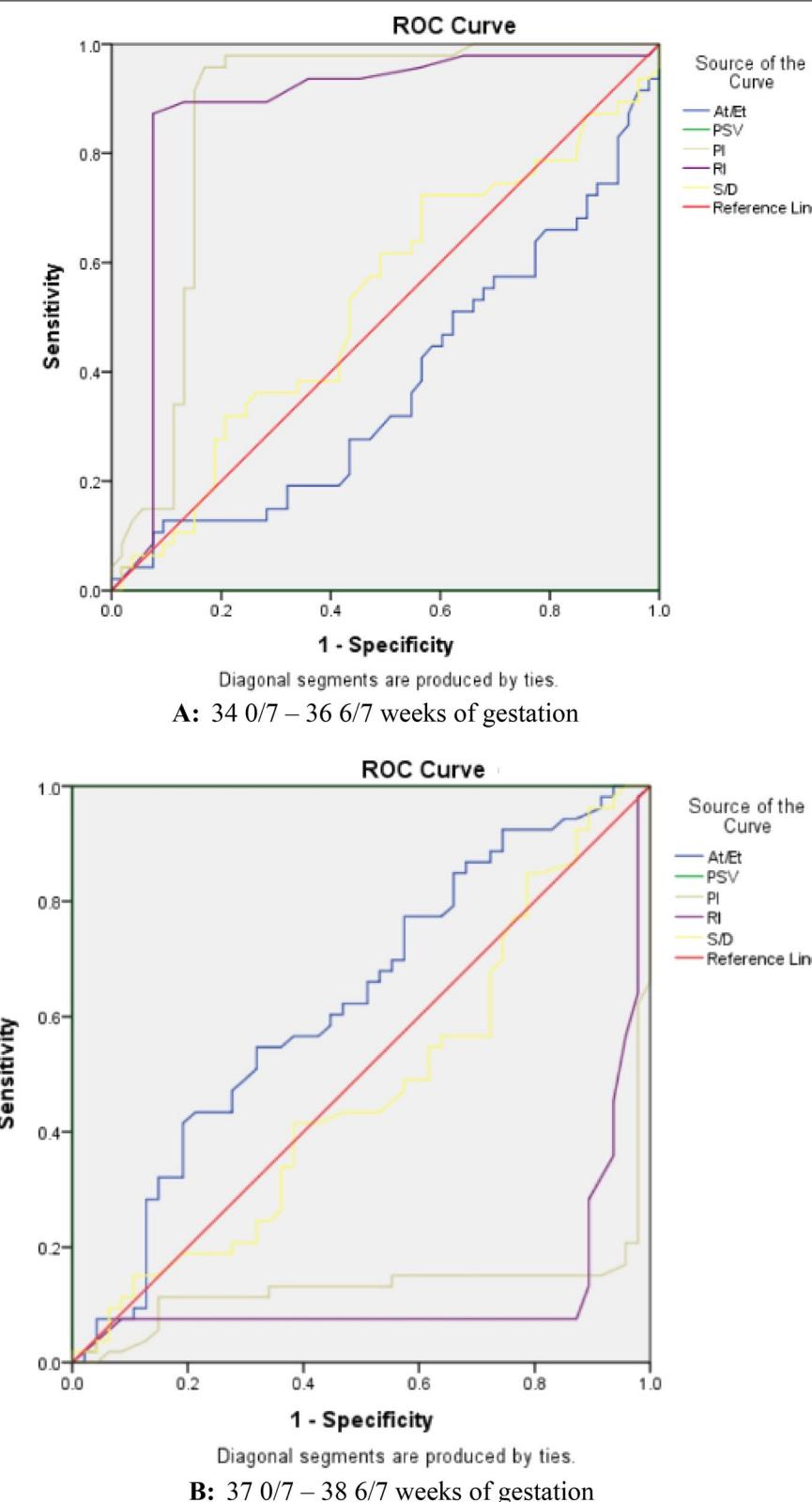


Fig. 2 Receiver operating curve (ROC) analysis. **A** 34 0/7–36 6/7 weeks of gestation. **B** 37 0/7–38 6/7 weeks of gestation

Table 4 Correlation of MPA Doppler indices with advancing gestational age

	G AGE	At/Et	PSV	PI
Spearman's rho				
G AGE	Correlation Coefficient	1.000	0.229	0.973
	Sig. (2-tailed)	–	0.022	0.000
	N	342	342	342
At/Et	Correlation Coefficient	0.229	1.000	0.240
	Sig. (2-tailed)	0.022	–	0.016
	N	342	342	342
PSV	Correlation Coefficient	0.473	0.240	1.000
	Sig. (2-tailed)	0.000	0.016	–
	N	342	342	342
PI	Correlation Coefficient	–0.317	–0.017	–0.355
	Sig. (2-tailed)	0.001	0.864	0.000
	N	342	342	342
RI	Correlation Coefficient	–0.313	0.103	–0.020
	Sig. (2-tailed)	0.901	0.309	0.845
	N	342	342	342

and specificity of RI was 100% and 94.2%, respectively, for the given cut off but in our study the sensitivity and specificity of RI was less as compared to At/Et ratio and moreover their study included only term infants and other pulmonary Doppler indices were not studied. Yassin et al. [21], in their study of 143 eligible foetuses concluded that MPA PI and RI were significantly higher and At/Et was significantly lower in foetuses diagnosed with RDS compared with those without using multimodality approach like 3D lung ultrasound, lung-to-liver intensity ratio tissue histogram and pulmonary artery Doppler. However, these methods are not yet widely used as the technique is too complicated for routine clinical practice. Schenone et al. [22] concluded that TDx-FLM-II assay (a quantitative measurement of ratio of surfactant to albumin in amniotic fluid assessed by amniocentesis) and MPA At/Et ratio showed positive correlation, which suggests that an increase in At/Et ratio relates to a lung which was more mature and hence lowering the risk of developing neonatal RDS, which matched the results of our study. However, in our study we did not correlate our findings with parameters measured within the amniotic fluid.

Contrary to the results of our study, Azpurua et al. [23] reported an inverse correlation of At/Et ratio and Lecithin/Sphingomyelin ratio which is widely considered as a marker of lung maturity and is obtained by amniocentesis. However, they did not account for the association between At/Et and neonatal RDS and also their sample of 29 foetuses was a considerable limitation with RDS

diagnosed in only one infant. Such an inverse correlation between At/Et ratio and RDS was also shown in the study done by Kim et al. [24].

In our study, the analysis of PSV, S/D ratio, PI and RI suffered from lower sensitivity and specificity to predict the occurrence of RDS compared to At/Et ratio which showed higher values of sensitivity and specificity. Besides being painless and non-invasive, MPA At/Et ratio shows high sensitivity and specificity, whereas FLM assessed by amniocentesis-based tests though reported high sensitivity had major flaw of low specificity [25].

To our existing knowledge, there are very limited studies available about the use of MPA Doppler Indices in assessing the occurrence of postnatal RDS and this is the first novel large-scale study conducted on the Indian population which aimed at providing an affordable and acceptable method in predicting the development of neonatal RDS. Our study is strengthened by the establishment of reference mean values for a series of Doppler velocity variables in the foetal MPA from 34 0/7 to 36 6/7 weeks of gestation and 37 0/7–38 6/7 weeks of gestation. We were further able to give a particular cut off value for AT/ET ratio, the selected variable of the foetal MPA Doppler indices, in above-mentioned gestational age during which time the prediction of RDS will aid in further management of foetuses.

Limitations of our study

Pregnant women with co-morbidities like hypertension and diabetes mellitus were excluded in our study, and the role of foetal MPA Doppler indices in predicting the RDS outcome would be of great help in this population, thus warranting further studies.

There were relatively less number of patients in our study who were successfully examined to demonstrate the association between foetal MPA Doppler waveforms and RDS at an interval of every two weeks of gestational age interval and longitudinal assessment of such measurements within the same foetuses has to be further studied in detail.

We did not correlate our findings with L/S ratio, thus warranting further studies.

Conclusions

The non-invasive prediction of FLM may be useful in determining the optimal timing of delivery for high-risk pregnancies. It is well accepted by patients because USG examination is non-invasive, cost-effective, uses non-ionizing radiations and is a widely used diagnostic tool in pregnancy. Moreover, foetal MPA Doppler can routinely be done as part of regular third trimester scan.

We recommend patients having foetus with above-mentioned cut-off for At/Et ratio, to be managed in a

well-equipped tertiary care centre with advanced ventilatory support. This approach greatly reduces the risks associated with amniotic fluid analysis for assessing FLM and in this way, we expect that this current test will lead to a decrease in neonatal morbidity and mortality, thereby improving neonatal outcome with a reduction in total medical cost related to neonatal care.

Abbreviations

AFI: Amniotic fluid index; At/Et ratio: Acceleration time/ejection time; EFW: Estimated foetal weight; FLM: Foetal lung maturity; GA: Gestational age; MPA: Main pulmonary artery; NBW: Neonatal birth weight; PI: Pulsatility index; PSV: Peak systolic velocity; RDS: Respiratory distress syndrome; RI: Resistivity index; S/D ratio: Systolic/diastolic.

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Author contributions

Dr VK and Dr AP were involved in data collection, analysis and interpretation and wrote the primary manuscript. Dr MSK and Dr SAR aided in designing the study and optimizing the study methodology. Dr RHC and Dr DKB performed the final revision and supervision. All authors offered meticulous aid in writing and editing the final manuscript. All authors read and approved the final manuscript.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by Ethics committee Bangalore medical college and research institute, approval number BMCR/PS/184/2020-21, and copy has been enclosed in attachments too. All patients signed a written consent that explained the procedure involved in the study.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that we have no conflicts of interest.

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