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Prediction of Lung maturity with Fetal breathing movement and Pulmonary artery Doppler Indices

Mostafa Abdulla Elsayed, A.I.El-Mashed, A.F.Yassin and Hatem Elgendy Abd Elsalam
Obstetrics and Gynecology Department, Faculty of Medicine, Benha University, Benha, Egypt
E-mail: Abdulrahman.fathy21@fmed.bu.edu.eg

Abstract

Background: A great effort has been made to predict fetal lung maturity to determine when a fetus is likely to develop neo-natal complications. The fetal pulmonary artery Doppler velocimetry may be useful to predict FLM. The aim of this work was to predict Lung maturity with fetal breathing movements and Pulmonary artery Doppler indices, the outcome measures will be correlated with respiratory distress syndrome (RDS) and admission in neonate intensive care unit. Methods: This cross-sectional study was carried out on 66 pregnant women had a singleton pregnancy with gestational ages from 34-36 weeks admitted in the unit for inevitable preterm labour. Neonates were further subdivided in to two groups regarding RDS: Group I without RDS included 42 cases and Group II with RDS included 16 cases. All patients were subjected to clinical examination, Spectral Doppler ultra-sound was used to obtain fetal main pulmonary artery waveforms, fetal biometry. Results: It was found that there was a significant positive correlation between HC and BPD, AC and HC, PSV and FL, S/D and BPD, PI and BPD, RI and HC, AT/ET and FL, and AT/ET and PSV. And there was significant negative correlation between FL and BPD, PSV and BPD, PSV and HC, PI and PSV, AT/ET and BPD, AT/ET and HC, and AT/ET and PI. PI, RI, PSV, AT/ET, BPD, HC and FL were significant predictors for the fetal lung maturity. Conclusions: Ultrasound evaluation of Fetal Mean Pulmonary Artery Doppler can be used as a rapid non-invasive accurate method for prediction of fetal lung maturity and neonatal respiratory distress syndrome, PI, RI, PSV, AT/ET, BPD, HC and FL can be used for prediction of fetal lung maturity.

Keywords: Doppler Indices, Fetal breathing movement, Lung maturity, Pulmonary artery.

1. Introduction

A great effort has been made to predict fetal lung maturity to determine when a fetus is likely to develop neo-natal complications as a result of pulmonary immaturity. Several methods to evaluate fetal lung maturity have been described, and the -standard of care today involves performing an amniocentesis. Amniocenteses carry risks and complications in approximately 0.7% of cases; such complications include preterm labor and de-livery, preterm premature rupture of membranes, placental abruption, and feteomaternal hemorrhage. Based on previous studies demonstrating a correlation between advancing gestational age and fetal pulmonary artery Doppler waveform acceleration/ejection time and between the latter and fetal lung maturity testing in amniotic fluid [1].

Neonatal respiratory distress syndrome (RDS) refers to respiratory compromise presenting at or shortly after delivery related to a deficiency of pulmonary surfactant, a naturally occurring phospholipid required to decrease surface tension within the alveoli to prevent alveolar collapse [2].

RDS remains a major cause of neonatal morbidity and mortality. However, not all infants are at equal risk, as the pulmonary system is among the last of the fetal organ systems to become functionally mature. As such, RDS is primarily, although not exclusively, a disease of premature infants, with an incidence and severity highly dependent on gestational age (GA) [3].

Given the importance of RDS as a cause of neonatal morbidity and mortality, even in late preterm deliveries, a number of biochemical tests have developed to predict the risk of RDS and obstetric care providers in delivery timing. These tests, including, among others, the (L/S) ratio and the presence or absence of phosphatidylglycerol (PG), require amniocentesis, followed by direct or indirect measurements of the surface-active properties of surfactant phospholipids secreted by the fetal lungs into the amniotic fluid [4].

The American College of Obstetricians and Gynecologists recommends that fetal pulmonary lung maturity should be confirmed in a low-risk singleton pregnancy if delivery is being contemplated before 39 weeks of gestation. A noninvasive test for fetal lung maturity (FLM) would be useful to minimize the need for -invasive testing and more acceptable to women [5].

The fetal pulmonary artery Doppler velocimetry may be useful to predict FLM. It was based on number of observations. First, the sonographic echogenicity of the fetal lung changes in a predictable pattern throughout pregnancy, which corresponds to morphologic and functional changes in fetal lung development with increasing GA [6].

Second, pulmonary artery Doppler velocimetry has previously been used in an attempt to identify fetuses at risk for pulmonary hypoplasia, albeit with mixed results. Third, pulmonary artery Doppler velocimetry studies have shown that neonates with RDS have increased pressure in their pulmonary vasculature, which decreases after treatment with artificial surfactant. Last, fetal pulmonary artery flow velocity (FPAF) waveforms have been measured throughout normal pregnancy and have been shown to change with advancing GA [4]. The aim of this work is to predict Lung maturity with fetal breathing movements and Pulmonary artery Doppler indices, the outcome measures will be correlated with RDS and admission in neonate intensive care unit.

2. Patients and Methods

This prospective cross-sectional study was carried out on 66 pregnant women attending our ultrasound unit for clinically indicated fetal lung maturity at Benha University Hospital and had a singleton pregnancy with an accurate GA were included and consented to participate in this study with gestational ages from 34-36 weeks admitted in the unit for inevitable preterm labour and was sonographically evaluated for the pulmonary artery indices and fetal breathing movement.

An informed written consent was obtained from the patient or relatives of the patients. The study was done after approval from the Ethical Committee on research involving human subjects of Benha Faculty of Medicine.

Exclusion criteria were patients who refuse participating in this study, a known fetal chromosomal or major structural abnormality, patients who received corticosteroids for fetal maturation, patients in whom the amniotic fluid was noted to be bloody or meconium-tinged and fetuses discovered to have structural anomalies after delivery.

Neonates were further subdivided in to two groups regarding RDS: Group I without RDS included 42 cases and Group II with RDS included 16 cases.

All patients were subjected to full history taking, clinical examination including pelvic area tenderness, extremities and back, neuromuscular; and pelvic evaluation - speculum and bimanual examination, clinic pelvimetry, uterine size, heart rate of fetus, and cervical check from 36 to 39 weeks. Spectral Doppler ultra-sound was used to obtain fetal main pulmonary artery waveforms. Additionally, the gestational age was confirmed using fetal biometry, and the amniotic fluid index, estimated fetal weight, and fetal heart rate was recorded.

Imaging:

By using Doppler US, the patients were placed in the supine decubitus position with a slight inclination (<45°) for maternal comfort. The sample volume gate was kept between 2 and 3 mm and was placed immediately distal to the pulmonary valve. The minimum required for this study consisted of 3 screens of waves of the main pulmonary artery.

The angle of insonation was maintained at less than 30 degrees. Once the waves were obtained, the fetal main pulmonary artery acceleration time (FMPAT) in milliseconds was measured in at least six waves and an average was calculated. Acceleration and ejection times of 3 representative waveforms from any of the above-mentioned 3 screens were obtained, and the average was used for analysis.

The mean pulmonary artery MPA Doppler waveform appeared with its characteristic shape (sharp systolic peak blood flow with a needle-like appearance, commonly referred to as a 'spike and dome' pattern). A small notch of reversed flow was also seen at the end of the systole. The characteristic shape of MPA waveform was important to differentiate it from the wave of the ductus arteriosus, which was rounded, fuller and triangular in shape with greater diastolic flow.

After the optimal fetal MPA waveform was obtained, relevant Doppler velocity variables were manually traced three times and the average was taken. The variables included the systolic/diastolic (S/D) ratio, pulsatility index (PI), resistance index (RI), PSV and the At/Et ratio.

To obtain the At/Et, the time interval from the beginning of the ventricular systole to the achievement of peak velocity (At) was divided by the time interval from the beginning to the end of ventricular systole (Et). Diagnosis of neonatal RDS Upon delivery, the route of delivery was recorded as well as the neonatal sex. A single paediatrician, from the authors' team, who was blinded to the fetal MPA Doppler measurements, handled the neonate. Neonatal birth weight (NBW) and Apgar score (at 1 and 5 min) were recorded.

The diagnosis of RDS was based on clinical signs of respiratory distress, supplemental oxygen requirement of 0.4 or greater for at least 24 h and typical chest X-ray findings with reticulogranular patterns, and ground glass appearance. As with postnatal breathing, FBMs were centrally organized rhythmic contractions of the diaphragm, but may also involve other skeletal muscles such as those of the chest wall and upper respiratory tract. Finally, MPA (acceleration time, ejection time, pulsatile index and FBM) was correlated to APGAR score, RDS and neonatal incubation a time of delivery.

Sample Size Calculation

Sample size were 66 Sample, were calculated using Open Epi program with confidence level 95% and power 80%. 8 cases underwent the ultrasound but did not attend at the time of delivery.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

3. Results

Total cases were 58 (100%). Control without RDS were 42(72.4%), while cases with RDS were 16(27.6%). There was no statistically significant difference between neonates without and with RDS regarding age, and BMI (P > 0.05). While there was statistically significant difference between neonates without and with RDS regarding parity. 14 (87.5%) of RDS cases were born for PG. There was statistically significant difference between neonates without and with RDS regarding weight and gender (P =0.004). Table 1

Regarding Ultrasound fetal data, there was no statistically significant difference between neonatal without and with RDS regarding HC and FL, BPD, AC and AFI (P > 0.05). Regarding MPA Doppler findings, there was statistically significant difference between neonates without and with RDS regarding PI, RI and AT/ET (P < 0.05). PI and RI were significantly higher in neonates with RDS compared to neonates without RDS, but AT/ET was significantly lower in neonates with RDS compared to neonates without. There was no statistically significant difference regarding PSV and S/D (P > 0.05). Table 2

It was found that there was a significant positive correlation between HC and BPD, AC and HC, PSV and FL, S/D and BPD, PI and BPD, RI and HC, AT/ET and FL, and AT/ET and PSV. And there was significant negative correlation between FL and BPD, PSV and BPD, PSV and HC, PI and PSV, AT/ET and BPD, AT/ET and HC, and AT/ET and PI. Table 3

PI, RI, PSV, AT/ET, BPD, HC and FL were significant predictors for the fetal lung maturity. The sensitivity of PI was 72.0%, while specificity was 69.0% and accuracy was 70.0% at cut off point =2.5. The RI has sensitivity 67.0%, specificity 65.0% and accuracy 66.0% at cut off value 0.74. The PSV sensitivity was 81.0%, specificity was 84.0% and accuracy 83.0% at cut off value 66, while AT/ET sensitivity was 98.0, specificity was 92.0% and accuracy was 95.0% at cut off value 0.3. The sensitivity of BPD was 72.0%, specificity was 67.0% and accuracy was 69.0% at cut off value 37.0, while the HC had sensitivity 75.0%, specificity 70.0 and accuracy 72.0% at cut off value 36.2. The FL sensitivity was 72.0%, specificity was 65.0% and accuracy was 67.0% at cut off value 37.5. Figure (1)

Table (1) Comparison between neonates without and with RDS regarding maternal demographic data and neonatal weight and gender.

			Without RDS Group I (42)		**With RDS Group II (16)**		**P value**
Maternal		**Age**	28.78 ± 6.05		29.24 ± 5.89		0.3090
			No	**%**	**No**	**%**	
	Parity	**PG**	10	23.8	14	87.5	**0.000****
		MG	32	76.2	2	12.5	
		BMI	26.45± 2.99		25.19 ± 2.57		0.064
Neonatal		**Weight (kg)**	3.20 ± 0.28		3.07 ± 0.36		**0.004***
	Gender	**Male**	8	19.0	10	62.5	**0.004***
		Female	34	80.9	6	37.5	

Data are presented as mean ± SD or frequency (%). BMI: Body mass index, *: statistically significant as P value <0.05

Table (2) Comparison between neonatal without and with RDS regarding Ultrasound fetal data, MPA Doppler findings.

	Without RDS Group I	With RDS Group II	P value
BPD	38.2 ± 2.0	38.81 ± 1.29	0.098
HC	37.2 ± 0.64	37.59 ± 0.88	0.107
FL	39.2 ± 1.0	39.62 ± 0.77	0.28
AC	38.6 ± 1.0	39.02 ± 0.88	0.38
AFI	12.0 ± 1.3	13.07 ± 1.24	0.25
PSV	67.1 ± 3.30	66.9 ± 3.12	0.116
S/D	6.4 ± 1.5	6.11 ± 1.28	0.725
PI	2.7 ± 0.88	3.06 ± 1.01	**0.006***
RI	0.72 ± 0.13	0.85 ± 0.10	**0.042***
AT/ET	0.39 ± 0.01	0.27 ± 0.03	**0.013***

Data are presented as mean ± SD or frequency (%). BPD: Biparietal diameter, HC: Head circumference, FL: Femur length, AC: Abdominal circumference, AFI: Amniotic fluid index. PSV: Peak systolic velocity, S/D: systolic/diastolic ratio, PI: Pulsatility index, RI: Resistive index, AT/ET: Acceleration time/ejection time *: statistically significant as P value <0.05

Table (3) Correlation between different parameters and occurrence of RDS.

		BPD	HC	FL	AC	AFI	PSV	S/D	PI	RI
HC	**r**	0.232								
	P	**0.001****								
FL	**r**	-0.143	-0.058							
	P	**0.043***	0.414							
AC	**r**	0.119	0.165	0.065						
	P	0.093	**0.019***	0.362						
AFI	**r**	0.041	0.051	0.059	0.071					
	P	0.567	0.475	0.408	0.321					
PSV	**r**	-0.141	-.200	0.218	0.047	0.047				
	P	**0.047***	**0.005***	0.002*	0.507	0.506				
S/D	**r**	0.139	-0.009	0.072	0.080	0.017	-0.026			
	P	**0.05***	0.903	0.312	0.257	0.811	0.718			
PI	**r**	0.153	0.125	0.026	-0.013	0.021	-0.147	-0.071		
	P	**0.030***	0.079	0.719	0.858	0.769	**0.038***	0.318		
RI	**r**	- 0.045	0.145	-0.018	0.059	-0.028	-0.074	-.039	-.006	
	P	0.526	**0.041***	0.805	0.411	0.699	0.296	0.584	0.928	
AT/ET	**r**	-0.251	-0.316	0.215	0.065	0.090	0.402	-0.043	-0.198	-0.051
	P	**0.000***	**0.000***	**0.002***	0.359	0.205	**0.000***	0.550	**0.005***	0.477

BPD: Biparietal diameter, HC: Head circumference, FL: Femur length, AC: Abdominal circumference, AFI: Amniotic fluid index. PSV= Peak systolic velocity, S/D: systolic/diastolic ratio, PI: Pulsatility index, RI: Resistive index, AT/ET: Acceleration time/ejection time. r= person correlation coefficient *: statistically significant as P value <0.05

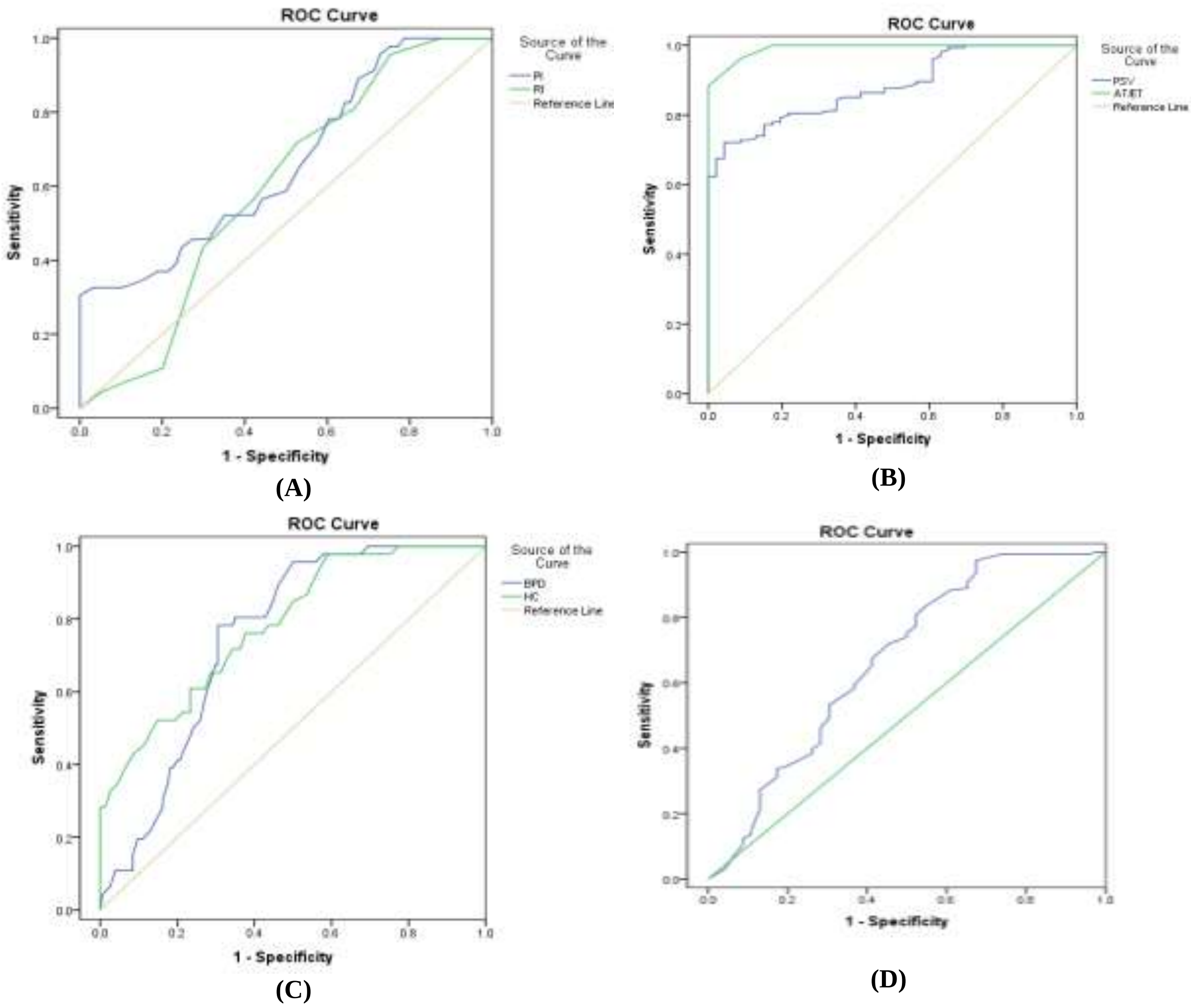

Fig. (1) ROC curves (A) for prediction value of PI, and RI to predict the fetal lung maturity. (B) for prediction value of PSV and AT/ET to predict the fetal lung maturity (C) prediction value of BPD and HC to predict the fetal lung maturity. (D) prediction value of FL to predict the fetal lung maturity.

4. Discussion

Respiratory distress syndrome (RDS) is one of the most common causes of neonatal respiratory failure and neonatal death. It was believed that RDS is mainly found in premature infants; however, great awareness of RDS has led to its more frequent diagnosis in term neonates [7].

This study showed no statistically significant difference between neonates without and with RDS regarding age, and BMI ($P > 0.05$). While there was statistically significant difference between neonates without and with RDS regarding parity. Alkashty et al. [8] reported that, there was no statistical significance between the collected demographic data (maternal age, gravidity, and parity) and RDS in cases of severe pre-eclampsia despite gestational age at the time of termination which has a statistical significance with the development of fetal RDS in cases of severe pre-eclampsia.

The current study revealed that, there was no statistically significant difference between neonatal without and with RDS regarding HC and FL, BPD, AC and AFI ($P > 0.05$). Alkashty et al. [8] reported that, there was a statistically significant inverse relationship between 2D Ultrasound findings as regard BPD, FL, AFI and IUGR, and RDS among the cases being studied.

Gilbert and Danielsen [9] cited that prematurity linked to poor neonatal outcomes (RDS, IVH, NEC, and CHA) was significantly influenced by IUGR in the third trimester.

In the present study, there was statistically significant difference between neonatal without and with RDS regarding PI, RI and AT/ET ($P < 0.05$) while there was no statistically significant difference regarding PSV and S/D ($P > 0.05$).

Abd elkhalik et al. [10] revealed that in compare to fetuses who have not develop neonatal RDS, fetuses that developed RDS had significantly l0wer At/Et and PSV and higher

PI and RI. This means that f0etuses who develop RDS have higher pulm0nary vascular resistance and pressure and l0wer pulm0nary blood fl0w c0mpared with fetuses that do not develop RDS.

But, Kim et al. [11] found that the median At/Et ratio in the fetal pulmonary artery Doppler was significantly higher in those fetuses that subsequently developed neonatal RDS compared with those that did not.

The RI has sensitivity 67.0%, specificity 65.0% and accuracy 66.0% at cut off value 0.78.

The PSV sensitivity was 81.0%, specificity was 84.0% and accuracy 83.0% at cut off value 45.0, while AT/ET sensitivity was 98.0, specificity was 92.0% and accuracy was 95.0% at cut off value 0.32.

Scopesi et al. [12] did a study to relate umbilical artery RI Doppler velocimetry to fetal and neonatal distress to establish whether umbilical artery Rl is a predictor of RDS and assess which fetal parameter is the best predictor of neonatal respiratory distress syndrome. They concluded that increased UA RI values (> 0.70) can be considered cut-off value that can predict which fetuses are at low/high risk for respiratory disorders and Doppler velocimetry analysis can provide more reliable information about fetal conditions and predict in which cases timing of delivery and unit care admission should be programmed.

Our study results shows that an AT/ ET cut of point of 0.30 can predict the development of neonatal RDS with a high sensitivity, specificity, and accuracy (98.0%, 92.0%, and 95.0% respectively). The best cutoff of AT/ET ratio in diagnosis of respiratory distress among our studied neonates was < 0.283 with area under curve 0.868 with sensitivity 82.4%, specificity 97.6%, positive predictive value (PPV) 87.5%, negative predictive value (NPV) 96.4% and accuracy 95% (p< 0.05) .The ability of S/D ratio , PI , RI and PSV to predict RDS development had the same sensitivity but lower specificity compared with that of At/Et .These results are consistent with prior studies at similar Gas [13-15].

Schenone and his colleagues [1] found a positive correlation between ratio in fetal MPA and TDx-FLM-II in amniotic fluid which means that an increased At/Et is associated a more mature lung and a less risk of developing RDS, which supports our findings, they demonstrated that a PATET cutoff of 0.3149 provides a sensitivity of 73%, specificity of 93% predicting TDx-FLM II results, with no study of clinical end points of fetuses and development of RDS.

However, Guan study [16] has shown that Fetal MPA Doppler waveforms can be measured throughout gestation and can be used as a safe and reproducible technique for the assessment of the fetal pulmonary circulation but additional large prospective clinical trials are needed to better examine the relationship between fetal MPA Doppler waveforms and neonatal RDS, to investigate how this relationship is affected by gestational age, and to determine whether this is true also of fetuses with threatening delivery in the late preterm (34–37 weeks) and early term period (37–39 weeks). These results match with our study, but here our study shows that also pulmonary RI, PSV show statically significant correlation. MPA At/Et and PS were positively correlated, whereas RI was inversely correlated with development of RDS, the strongest correlation was found as regarding AT/ET and the cut point of 0.32 is achieved by a high sensitivity and specificity.

The sensitivity of BPD was 72.0%, specificity was 67.0% and accuracy was 96.0% at cut off value 37.0. Regarding the BPD as a marker for fetal lung maturity, correlation of BPD > 90 mm with a positive shake test (in amniocentesis) showed 100% predictivity (Pallavi et al., 2017).

5. Conclusions

Ultrasound evaluation of Fetal Mean Pulmonary Artery Doppler can be used as a rapid noninvasive accurate method for prediction of fetal lung maturity and neonatal respiratory distress syndrome, mean pulmonary artery Doppler indices, as acceleration time / ejection time, Resistance index, Peak systolic velocity, and Pulsatility index indices can be used for prediction of fetal lung maturity. The strongest correlation was found as regarding acceleration time / ejection time.

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