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Predictive Value of Fetal Pulmonary Artery Doppler in Neonatal Respiratory Distress Syndrome

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ABSTRACT

Background: Respiratory distress syndrome [RDS] is a major concern in preterm neonates, contributing significantly to infant morbidity and mortality. Fetal pulmonary artery Doppler has emerged as a potential tool for predicting the risk of RDS in neonates before birth.

Aim of the work: This study aims to investigate the predictive value of fetal pulmonary artery Doppler in identifying neonates at risk of developing respiratory distress syndrome.

Patients and Methods: A prospective cohort study was conducted involving a total of 100 pregnant women in their third trimester. Fetal pulmonary artery Doppler ultrasound measurements were performed on the participants. Neonates underwent clinical and radiological assessment for RDS in first 72 hrs. Accuracy of Doppler indices for predicting RDS was analyzed.

Results: Neonates with RDS exhibited significantly lower values of At/Et, PSV, and S/D, alongside higher values of PI and RI. A significant negative correlation was found between At/Et, PSV, and S/D, and a positive correlation between RI and oxygen therapy duration. At/Et, PSV, PI, and RI demonstrated high sensitivity and specificity for predicting RDS at their respective cutoff values.

Conclusion: Fetal pulmonary artery indices effectively predict lung maturity and neonatal RDS; however, combining AT/Et with other predictors is recommended to maintain specificity across different gestational ages.

Keywords: Doppler Ultrasonography; Pulmonary Artery; Newborn Respiratory Distress Syndrome.

INTRODUCTION

Respiratory distress syndrome [RDS] has emerged as a leading cause of respiratory failure and neonatal mortality among infants. As awareness of RDS increases, previously believed to primarily affect preterm newborns, the syndrome is now more frequently identified in full-term neonates [1].

A major factor contributing to newborn morbidity and mortality is RDS, associated with deficiencies in pulmonary surfactant. The pulmonary system is the final organ system in a developing fetus that necessitates additional time in utero for physiological maturation [2].

Assessment of fetal lung development represents a paramount objective in obstetrical practice. Traditionally, the maturation of fetal lungs has been gauged through amniocentesis, involving the analysis of the proteins and lipids present in the amniotic fluid. However, amniocentesis is an invasive procedure warranted for specific indications, and while these tests exhibit high sensitivity, their specificity is relatively low in clinical practice [3].

Throughout gestation, the development of the pulmonary circulation mirrors the growth of the lungs. This process involves an expansion in smooth muscle tissue, an increase in the number of pulmonary vessels, and a slight reduction in the vascular resistance of pulmonary arteries. These changes culminate in a progressive rise in pulmonary blood flow [4].

Doppler velocimetry provides a rapid and non-invasive method to assess fetal pulmonary circulation. Researchers have employed Doppler velocimetry to analyze blood flow in the main pulmonary artery and its peripheral branches [5].

Research has demonstrated a correlation between increasing fetal gestational age and fetal lung maturity, as assessed by testing amniotic fluid, with the ratio of acceleration time to ejection time [At/Et] in the fetal pulmonary artery [6].

This study aimed to investigate the utility of Doppler signals from the fetal main pulmonary artery as a predictive tool for anticipating the onset of neonatal RDS.

PATIENTS AND METHODS

This study involved a prospective cohort of 100 pregnant women who were receiving care at the Obstetrics and Gynecology Department of Al-Azhar Faculty of Medicine [New Damietta] from January 1st to June 30th, 2021.

Inclusion criteria: Participants must deliver a single baby at a gestational age between 37 and 38 weeks. Accurate determination of gestational age is required, either by utilizing a specific last menstrual cycle in alignment with second-trimester ultrasound or by dating based on a first-trimester ultrasound.

Exclusion criteria: Significant chromosomal disorders or structural abnormalities in the fetus, and maternal pregnancy complications including gestational diabetes and preeclampsia. Moreover, the administration of antenatal corticosteroids was not considered in this research.

Neonatal follow up: The newborn's birth weight [NBW] and their Apgar scores [at 1 and 5 minutes] were recorded, and the duration of time that the infant spent in critical care was documented. The diagnosis of Neonatal RDS was based on a combination of clinical presentation, radiographic findings, and available laboratory data. Infants were considered to have RDS if they exhibited signs of respiratory distress shortly after birth, such as tachypnea, nasal flaring, grunting, and chest retractions. In addition, chest X-rays were assessed for typical findings such as ground-glass appearance, air bronchograms, and decreased lung volume. Laboratory parameters including arterial blood gas analysis showing hypoxemia and hypercapnia also contributed to the diagnosis. The final diagnosis of RDS was made by the attending neonatologist based on these criteria.

Methodology

The research was conducted using a Voluson S10 ultrasound machine. Upon performing a standard ultrasound examination for assessing fetal parameters such as size, estimated weight, and amniotic fluid index, a thorough fetal heart assessment was carried out on a supine pregnant woman. Various views, including the three-vessel view, outflow leaflets, and four-chamber view, were utilized to scrutinize the fetal heart. The examination was performed with the fetus in a resting state and without movement during respiration.

During the examination, the examiner traced the main pulmonary artery [MPA] using specific landmarks until it was divided in half between the pulmonary valve and the branching point of the right and left main pulmonary arteries in the thoracic region. The pulsed Doppler sample gate

size was adjusted to 3 mm, while maintaining an insonation angle of 15°. Doppler gain and scale settings were optimized to accurately depict the peak systolic velocity [PSV] and early diastolic notch in the velocity waveform.

The distinctive "spike and dome" pattern of the MPA Doppler waveform, characterized by a sudden systolic peak followed by a tiny diastolic notch, was identified. Additionally, a minimal notch of reversed flow at the end of systole was observed. Differentiating the MPA waveform from the ductus arteriosus waveform, known for its triangular shape and rounded diastolic flow, was emphasized as a critical aspect of the examination.

The optimal foetal MPA waveform was generated initially, followed by the manual tracing of the necessary Doppler velocity variables three times with subsequent averaging of the outcomes. Several crucial factors, including the ratios of systolic/ diastolic [S/D], Pulsatility index [PI], resistance index [RI], peak systolic velocity [PSV], and the ratio of At/Et, were examined. To calculate the At/Et ratio, the duration [At] from the beginning of ventricular systole to the attainment of peak velocity was divided by the length [Et] of the ventricular chamber systole.

Sample size calculation: The sample size was determined utilizing an equation, resulting in a sample size of 80 participants at a 5% significance level and 80% power, in accordance with the formula [7]. The calculation incorporated a Z value of 1.96 for a 95% confidence level, with the anticipated rate of respiratory distress in neonates [p] established at 4% and a margin of error for reliability [d] set at 0.03.

Ethical consideration: An informed consent obtained from each patient, after full explanation of the study protocol. The Al-Azhar Faculty of Medicine [New Damietta] local research and ethics committee approved the study protocol.

Statistical Analysis: The SPSS program [Version 24] for Microsoft was used to code, process, and analyze the obtained data. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were calculated. For comparative analyses, independent t-tests were employed to assess differences between two independent groups, while chi-square tests were conducted to evaluate associations between categorical variables. Pearson correlation coefficients were calculated to determine the strength and direction of relationships between continuous variables. To assess the diagnostic performance of our primary predictors, receiver operating characteristic [ROC] curve analysis was performed, allowing for the calculation of sensitivity, specificity, and the area under the curve [AUC]. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

There is no statistically significant difference in maternal age, sex of the newborn, or labor characteristics between neonates with RDS and those without RDS [Table 1].

Regarding the APGAR scores at one minute and 5 minutes, there was no statistically significant difference between premature infants with RDS and those without RDS. However, neonates with RDS exhibited a significantly higher rate of admission to the neonatal intensive care unit [NICU] and were more likely to require oxygen therapy compared to neonates without RDS. Additionally, neonates with RDS had a statistically significantly lower birth weight than those without RDS. No significant differences were observed in maternal age, sex of the infant, or labor characteristics between the two groups [Table 2].

Neonates with RDS exhibit significantly lower values of At/Et, PSV, and S/D, and significantly higher values of PI and RI compared to those without RDS [Table 3].

Additionally, there is a statistically significant negative correlation between At/Et, PSV, and S/D, and a significant positive correlation between RI and the duration of oxygen therapy [Table 4].

The current study found that At/Et had a sensitivity of 94.4% and a specificity of 90.9% for estimating RDS at a cutoff level of 0.346. PSV demonstrated a sensitivity of 100% and a specificity of 100% for predicting RDS at a cutoff level of 74.45. PI showed a sensitivity and specificity of 100% for predicting RDS at a cutoff level of >2.35, and RI also had a sensitivity and specificity of 100% for predicting RDS at the defined cutoff level [Table 5].

Table [1]: Comparison of demographic data of the studied population

		RDS [n=11]	No RDS [n=89]	Test	P value
Maternal age [years]	Range	20-25	20-30	-0.437	0.663
	Mean ± SD	22.64 ± 2.06	22.93 ± 2.12		
Sex, n [%]	Female	5 [45.5%]	50 [56.2%]	0.455	0.500
	Male	6 [54.5%]	39 [43.8%]		
Labor, n [%]	Yes	2 [18.2%]	33 [37.1%]	1.537	0.215
	No	9 [81.8%]	56 [62.9%]		

Table [2]: Comparison of APGAR score, need for oxygen therapy, gestational age and neonatal birth weight of the studied population

		RDS [n=11]	No RDS [n=89]	Test	p-value
APGAR 1 min	**Range**	6-7	6-7	-0.098	0.923
	Median [IQR]	7 [1]	7 [1]		
	Mean ± SD	6.56 ± 0.50	6.55 ± 0.52		
APGAR 5 min	**Range**	7-9	8-9	2.156	0.05
	Median [IQR]	8 [1]	9 [1]		
	Mean ± SD	8.18 ± 0.59	8.54 ± 0.52		
Admission for O2 treatment	**Yes**	11 [100%]	29 [32.6%]	18.539	**< 0.001**
	No	0 [0%]	60 [67.4%]		
Admission duration [days]	**Range**	1 - 7	8 - 10	11.107	**< 0.001**
	Mean ± SD	9.00 ± 1.00	3.17 ± 1.70		
Neonatal birth weight [gm]	**Range**	11 [100%]	29 [32.6%]	13.968	**< 0.001**
	Mean ± SD	3479.29 ± 450.85	2751.18 ± 69.05		
Gestational age [weeks]	**Range**	37-38	37-38	1.818	0.080
	Mean ± SD	37.74 ± 0.44	37.09 ± 0.30		

Table [3]: Comparison of fetal pulmonary artery Doppler of the studied population

		RDS [n=11]	No RDS [n=89]	Test	p-value
Acceleration Time to Ejection Time	Range	0.33 – 0.35	0.34 – 0.42	-17.326	**<0.001**
	Mean ± SD	0.33 ± 0.01	0.39 ± 0.02		
Peak systolic velocity	Range	72.67 - 73.37	75.54 - 77.79	-30.481	**<0.001**
	Mean ± SD	73.02 ± 0.35	76.64 ± 0.51		
Pulsatility index	Range	1.68 - 2.23	2.48 - 2.61	22.527	**<0.001**
	Mean ± SD	2.52 ± 0.05	2.07 ± 0.14		
Resistance index	Range	0.80 - 0.83	0.73 - 0.77	18.508	**<0.001**
	Mean ± SD	0.82 ± 0.01	0.75 ± 0.01		
Systolic/diastolic ratio	Range	6.13 - 7.13	6.63 - 7.55	1.771	0.098
	Mean ± SD	6.94 ± 0.29	7.11 ± 0.37		

Table [4]: Correlation between the duration of oxygen therapy and fetal pulmonary artery Doppler parameters

	The duration of oxygen therapy	
	r	p-value
Neonatal birth weight	0.152	0.132
Acceleration Time to Ejection Time	-0.443	<0.0001
Peak systolic velocity	-0.519	<0.0001
Pulsatility index	-0.085	0.403
Resistance index	0.432	<0.0001
Systolic/diastolic ratio	-0.578	<0.0001

Table [5]: Sensitivity, specificity and cutoff value of At/Et, PSV, PI, RI and S/D for prediction of RDS

	Cutoff point	Area under curve	Std. Error	Sensitivity %	Specificity %	95% Confidence Interval	
						Lower Bound	Upper Bound
At/Et	<0.346	0.995	0.006	94.4%	90.9%	0.984	1.000
PSV	<74.45	1.000	0.000	100%	100%	1.000	1.000
PI	>2.35	1.000	0.000	100%	100%	1.000	1.000
RI	>0.785	1.000	0.000	100%	100%	1.000	1.000
S/D	<6.93	0.607	0.060	59.6%	54.4%	0.488	0.725

DISCUSSION

No statistically significant differences were observed between neonates with and without respiratory distress syndrome [RDS] regarding maternal age, newborn gender or mode of labor. Our findings are consistent with those reported by **Khalil *et al.*** [8], which indicated no significant variations in maternal age or parity between infants with and without RDS.

Similarly, a study conducted by **Alsheikh *et al.*** [9], which involved 120 singleton pregnant women, identified 16 cases [13.3%] of RDS among the newborns. The infants with RDS did not show significant differences in maternal age or parity compared to those without RDS.

The results of the present study indicate no statistically significant difference in APGAR scores at one and five minutes between neonates with RDS and those without it.

Our findings are consistent with those reported by **Büke *et al.*** [10], which revealed no significant differences in 5-minute APGAR scores between RDS-affected newborns and those unaffected. Conversely, **Abdelhamid *et al.*** [11] found statistically significant variations in 5-minute APGAR scores between neonates with RDS and those without the condition. Additionally, **Eldeeb *et al.*** [12] observed that neonates with RDS had notably lower APGAR scores at 5 minutes, lower birth weights, and a higher rate of admission to the NICU compared to healthy newborns [$p < 0.001$]. This discrepancy may be attributed to differences in the severity of the conditions at the time of assessment.

The current study demonstrated that neonates with RDS required more oxygen therapy and had significantly longer stays in the NICU compared to neonates without RDS.

Findings from a study by **Keshuraj *et al.*** [13] support our results, showing a marked difference in NICU admission rates, with 100% of RDS-positive newborns requiring hospitalization compared to only 33.2% of RDS-negative infants. Other common reasons for hospitalization included prenatal asphyxia [n = 53], neonatal hyperbilirubinemia [n = 31], hypoglycemia [n = 7], meconium aspiration [n = 5] and convulsions [n = 2].

Similarly, **Laban *et al.*** [14] identified significant differences in NICU admission criteria between the two groups. Some newborns with RDS required oxygen therapy for specific durations, ranging from 24 to 48 hours, before transitioning to alternative methods such as nasal prongs or head boxes. One infant required ongoing positive airway pressure for 48 hours before transitioning to nasal prongs, head box, and eventually room air over subsequent 24-hour periods.

In the present study, neonates with RDS exhibited significantly lower birth weights compared to those without RDS. However, there was no statistically significant difference in gestational age between neonates with RDS and those without.

In the study conducted by **Moety *et al.*** [15], fetuses that developed RDS showed higher amniotic fluid index values, lower estimated fetal weights on ultrasound, lower mean birth weights, and significantly shorter gestational ages at delivery. Similarly, **Li *et al.*** [16] reported that neonates in the NRDS group had significantly lower gestational ages at birth and birth weights compared to those in the non-NRDS group, which may be attributed to variations in sample sizes.

The prediction of neonatal RDS may be associated with the pulmonary artery resistance index [PA-RI] and fetal lung volume [FLV]. Changes in lung echogenicity, structure, and physiological development with advancing gestational age can affect the waveform patterns of prenatal pulmonary artery blood flow velocity. Following surfactant administration, infants with RDS have been observed to experience a decrease in Doppler-measured pulmonary artery pressures [17].

Our results indicated that neonates with RDS exhibited significantly higher pulmonary artery PI and RI, along with significantly lower ratios of At/Et, PSV, and S/D ratio compared to neonates without RDS. We also observed a significant inverse relationship between At/Et, PSV, and S/D, as well as a statistically significant inverse correlation between RI and the duration of oxygen therapy.

In a study by **Keshuraj *et al.*** [13], the average main pulmonary artery [MPA] At/Et ratio was notably lower in RDS-affected infants compared to the non-RDS group, with values of 0.2865 ± 0.039 versus 0.3357 ± 0.058 in late preterm infants, and 0.3155 ± 0.044 versus 0.3527 ± 0.056 in early term infants. The median MPA PI values were significantly higher in RDS-positive fetuses. Additionally, statistical analysis of mean MPA RI values revealed higher values in RDS-affected newborns, with values of 0.92 ±

0.16 versus 0.83 ± 0.08 [p < 0.05] in late gestation newborns, and 0.8 ± 0.02 versus 0.75 ± 0.07 [p < 0.05] in early term infants. Compared to the non-RDS group, PSV was significantly lower in RDS-positive fetuses, with values of 64.93 ± 1.88 versus 68.19 ± 0.06 cm/s in late preterm newborns, and 73.37 ± 0.56 versus 76.44 ± 0.12 cm/s in early term infants. No significant variations were observed in the S/D ratio between the two groups.

Additionally, **Taha *et al.*** [18] found that infants diagnosed with RDS exhibited markedly higher PI and RI values compared to infants without RDS [p = 0.025 and 0.036, respectively]. Peak systolic velocity [PSV] and the At/Et ratio were significantly lower in neonates with RDS compared to controls [p = 0.004 and 0.001, respectively] across both measurements. Notably, neonates with RDS displayed a significantly higher RI than their non-RDS counterparts [p = 0.048]. Furthermore, neonates with RDS demonstrated significantly lower PSV and At/Et ratios compared to neonates without RDS [p = 0.008 and 0.001, respectively].

Moety *et al.* [15] reported a considerable decrease in the main pulmonary artery [MPA] At/Et ratio in fetuses with RDS, compared to those without, with values of 0.209 ± 0.054 versus 0.332 ± 0.066 [p < 0.001]. MPA PI and RI were significantly higher in RDS-affected fetuses [2.27 ± 0.23 and 0.80 ± 0.11 cm/s versus 2.18 ± 0.23 and 0.76 ± 0.09 cm/s], while PSV was significantly lower in the RDS group [65.05 ± 5.33 versus 67.21 ± 4.80 cm/s; p = 0.002]. Minor differences were observed in the S/D ratio between the two groups.

Additionally, **Khalifa *et al.*** [19] found that MPA-PI and RI values were substantially higher in RDS-affected fetuses than in control fetuses, with values of 2.51 ± 0.33 and 0.90 ± 0.03 cm/s compared to 1.96 ± 0.20 and 0.84 ± 0.01 cm/s, respectively [p < 0.001 for both]. In contrast, the MPA At/Et ratio was notably lower in the RDS group, measuring 0.24 ± 0.04 versus 0.35 ± 0.04 [p < 0.001]. **Alsheikh *et al.*** [9] similarly reported that infants with RDS exhibited significantly higher pulmonary artery RI [0.88 ± 0.05 versus 0.83 ± 0.06; p = 0.001], PI [1.9 ± 0.2 versus 1.74 ± 0.23; p = 0.014], and peak systolic velocity [PSV] [88.1 ± 12.0 versus 77.4 ± 14.3; p = 0.005] compared to neonates without RDS. Furthermore, they noted a significantly lower pulmonary artery At/Et ratio in the RDS group [0.26 versus 0.31] compared to non-RDS infants.

In light of the findings from the current investigation, the At/Et ratio demonstrated a sensitivity of 94.4% and a specificity of 90.9% in identifying RDS at a threshold of 0.346, as determined by ROC curve analysis. PSV exhibited 100% sensitivity and specificity at a threshold of 74.45 for predicting RDS. For PI, sensitivity and specificity were both 100% when the threshold surpassed 2.35. Similarly, RI also showed 100% sensitivity and specificity for predicting RDS at a threshold above 0.785. The S/D ratio, at a cutoff of 6.93, displayed a sensitivity of 59.6% and a specificity of 54.4% in predicting RDS.

Guan *et al.* [20] discovered that using a gestational age-specific threshold at or below the fifth percentile, acceleration time [AT] could independently predict RDS with a sensitivity of 78.6% and an accuracy of 89.7%. The AT/Et ratio predicted RDS with a sensitivity of 71.4% and a specificity of 93.1%. Research by **Moety *et al.*** [15] reported that an AT/Et cutoff of 0.305 achieved an accuracy of 76.4% and a specificity of 91.6% in predicting neonatal RDS, with an area under the curve [AUC] of 0.899. However, pulmonary artery PI and RI demonstrated lower sensitivity and specificity in predicting RDS.

In the study conducted by **Li *et al.*** [16], the AUC value for the embryonic main pulmonary vein Doppler parameter AT/Et ratio in predicting neonatal RDS during pregnancy was 0.984 [95% CI 0.958-1.000]. The optimal cutoff value, determined by the highest Youden index, was 0.2175 for forecasting NRDS, achieving a specificity of 95.9% and an accuracy of 93.3%.

In a study by **Eldeeb *et al.*** [12], the authors identified that the acceptable area under the ROC curve for predicting RDS in newborns was 0.75. The pulmonary artery resistance index demonstrated a specificity of 82.95% and a sensitivity of 76.27%. Additionally, a fetal lung volume cutoff of 28 cm^3 was associated with a specificity of 65.91% and a sensitivity of 72.88%. When combining these two parameters, the predictive model exhibited enhanced reliability, resulting in an accuracy of 83%, a sensitivity of 100%, a specificity of 65.91%, a positive predictive value of 66.3%, and a negative predictive value of 100%.

Furthermore, **Keshuraj *et al.*** [13] aimed to prevent the development of RDS in preterm fetuses through Doppler imaging assessments. They established ROC curves and identified optimal cutoff values for the AT/Et ratio, with an area under the curve [AUC] of 0.883 [95% CI 0.810 to 0.956; $p < 0.05$] in late preterm infants and an AUC of 0.926 [95% CI 0.854 to 0.998; $p < 0.05$] in early term infants. For late preterm infants, the optimized cutoff value was determined to be 0.2865, resulting in specificity and sensitivity rates of 94.79% and 89.45%, respectively. Similarly, for early term newborns, the AT/Et ratio cutoff value was found to be 0.3155, with a specificity of 96.78% and a sensitivity of 93.22%.

Several limitations of this study warrant acknowledgment. Firstly, maternal comorbidities such as diabetes mellitus and hypertension were not accounted for in the analysis, which could potentially influence the relationship between fetal pulmonary artery Doppler measurements and neonatal RDS. This omission may have introduced confounding variables that could affect the validity of our findings. Secondly, the study did not include validation with other established predictors of RDS, such as the lecithin-to-sphingomyelin ratio, which could have provided a broader understanding of the predictive value of Doppler measurements. In addition, focusing solely on full-term infants means that the results may not be generalizable to preterm neonates, who are at a higher risk of developing RDS. Therefore, it is important to recognize that the generalizability of our conclusions to preterm populations may be limited. Future research should aim to address these limitations to enhance the robustness and applicability of the findings in clinical practice.

Conclusion: We have determined that fetal pulmonary artery indices exhibit a notable level of sensitivity and specificity in forecasting fetal lung maturity and the onset of neonatal RDS. While the AT/Et measurement of the main pulmonary artery proved to be markedly effective in distinguishing between fetuses that experienced RDS and those that did not, it is advisable to incorporate this measurement alongside other predictors. Relying solely on the AT/Et measurement may reduce specificity across various gestational ages.

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Conflict of Interest: None.

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