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" The Role of Doppler Waveforms measurements of the Fetal Main Pulmonary Artery in the Prediction of Neonatal Respiratory Distress Syndrome in diabetic pregnancies "

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ABSTRACT:

Objective: The purpose of this research is to investigate the potential significance of prenatal pulmonary artery Doppler indices as predictive indicators for the development of respiratory distress syndrome in infants born to mothers with diabetes.

Methods: The present cross-sectional research was carried out at the Department of Obstetrics and Gynecology, PortSaid Maternity Hospital, spanning from February 2022 to March 2023. We recruited diabetic mothers according to predetermined exclusion and inclusion criteria. Eligible women were subjected to complete history taking and examination. Fetal pulmonary artery doppler was done before delivery.

Results: This prospective study included 103 pregnant diabetic women, classified into two groups: group (1) included 50 diabetic women with preterm labor, and group (2) included 53 women with full-term gestation. The incidence of RDS in the preterm group (70%) was a highly significant difference ($p < 0.001$) in comparison with the full-term group (15.1%). Ultrasonographic Doppler parameters demonstrated significant difference ($p < 0.01$) in AT, AT/ET, PSV, and mean velocity, while ET, EDV, Pulsatility index and Resistive index showed statistically non-significant difference in comparison among 2 studied groups. The regression line showed a highly significant positive correlation among AT and RDS in both groups ($r = 0.8678$, $P = 0.0001$).

Conclusion: The major pulmonary artery in the fetus, the incidence of infant RDS was predicted by Doppler scans.

Keywords: maternal diabetes; respiratory distress; Doppler study; fetal pulmonary artery.

Introduction:

Neonatal respiratory distress syndrome (RDS) refers to a respiratory dysfunction that manifests either at the time of delivery or immediately afterwards. This factor is a leading contributor to both the incidence and fatality rates among newborns(1). Elective delivery at gestation <39 weeks was linked with an increased risk of RDS (2). High-risk pregnancy forces obstetricians to iatrogenic preterm birth, which increases the risk of RDS (3). This mandates fetal lung maturity (FLM) determination before delivery. Variable biochemical tests include lecithin/sphingomyelin ratio and phosphatidyl glycerol in the amniotic fluid. However, these tests require an amniotic fluid sample, which is an invasive procedure (4). It is associated with possible complications such as premature rupture of membranes, preterm birth, feto-maternal hemorrhage, placental abruption, or fetal death (5). Although amniocentesis for FLM is performed in the third trimester, complications are documented (6). Ultrasound markers of FLM are used in the third trimester. Fetal lung echogenicity changes during pregnancy, and variable predictive values were reported according to the technique employed (7). Recent studies evaluated the fetal main pulmonary artery's role in predicting FLM with comparable results to the clinical outcome or biochemical tests by amniocentesis (8). As the development of the fetal lung progresses, there is a concurrent growth in the pulmonary vasculature, an increase in the number of pulmonary arteries, and a reduction in pulmonary arterial resistance (9). The correlation between fetal gestational age and FLM tests in amniotic fluid may be observed by the evaluation of fetal pulmonary artery Doppler investigations, specifically the acceleration time/ejection time ratio (10), with evidence of a significant role in the prediction of RDS, especially in preterm neonates (11). However, its role in term infants was not evaluated properly (3). Accordingly, this research was conducted to evaluate the role of fetal main pulmonary artery Doppler studies in predicting fetal RDS in diabetic mothers.

Materials and methods:

The present cross-sectional research was undertaken in the Department of Obstetrics and Gynecology, PortSaid Maternity Hospital, spanning the period from February 2022 to March 2023. Diabetic moms were recruited based on predetermined inclusion and exclusion criteria:

- Inclusion criteria: a) maternal age 18- 45 years, b) singleton pregnancy, c) viable fetus, d) intact membranes, e) history of pregestational or gestational diabetes, f) gestational age ≥ 34 weeks.
- Exclusion criteria: a) women with unsure dates; b) known fetal anomalies, even if diagnosed after delivery; c) fetal growth restriction; d) other medical disorders with pregnancy; e) fetal congenital heart anomalies, even if diagnosed after delivery, f) antepartum hemorrhage, g) pregnancies complicated with polyhydramnios or oligohydramnios, and h) women refusing to participate in the study.

Eligible women were subjected to:

- Complete history taking, including age, parity, gestational age, residence, occupation, history of any chronic illness, and complete obstetric history.
- An obstetric ultrasound examination was conducted utilizing a convex probe with a frequency range of 3 to 5 MHz, specifically the Toshiba Aplio 500 model (S/N 28184086, manufactured in Japan). The objective of this study was to evaluate a range of fetal biometric parameters, such as biparietal diameter, head circumference, belly circumference, chest circumference, and femur length.Additionally, calculations were performed to determine the expected fetal weight, placental site, amniotic fluid volume, and amniotic fluid index.
- The Doppler investigation was conducted with an Acuson Sequoia 512 ultrasound machine manufactured by Siemens Medical Solutions, located in Mountain View, CA. The equipment was outfitted with a 4–6-MHz convex transducer. The sample gate was maintained at a width of 3 mm, while the insonation angle was limited to a maximum of 15°. The parameters of Doppler, including its gain and scale, were adjusted in order to optimize the visualization of the wave pattern, specifically highlighting the peak systolic velocity as well as the notch observed during early diastole. A trained operator conducted Doppler velocity waveform measurements of the major pulmonary artery (MPA) in the fetus after a regular prenatal sonographic evaluation. The pregnant participants had supine scanning, during which all fetuses exhibited sinus rhythm and were seen to be calm, with no observable fetal breathing movements.The fetal heart was examined at each level,

starting from the level of four-chamber, the right and left ventricular outflow tracts, and lastly, the three-vessel view to rule out any congenital anomalies of the heart. The main pulmonary artery was seen in the transverse view of the fetal chest with complete ribs on both sides while the fetus is completely quiet. Then, the measurement point was reached after the pulmonary artery valve and before the origin of the left and right pulmonary arteries. The fetal MPA was visualized after magnifying the axial part of the thoracic cavity at the 4- 4-chamber view level (11).

- Doppler investigations were conducted inside the fetal MPA throughout the study. The waveforms exhibited a distinct "spike and dome" pattern, characterized by a notch observed near the termination of the systolic phase. Doppler measurements were done manually. Three measures were recorded, and the average was used in the final analysis.
- Doppler Parameters encompass various measurements including acceleration time (AT), period from the base to the top of the peak systolic velocity (PSV), ejection time (ET) which represents the duration of ventricular systole, end-diastolic maximum velocity (EDV), mean velocity (MV) which denotes the time-averaged maximum velocity, pulsatility index (PI) calculated as the ratio of (PSV multiplied by 2) to EDV divided by MV, and resistance index (RI) calculated as the ratio of (PSV minus EDV) to PSV. The AT/ET ratio can be estimated based on these measurements. Automated traces were used to assess several Doppler parameters, including the peak blood flow velocity attained during systole (PSV), the pulsatility index (PI), and the resistance index (RI). The high-pass filter was configured at a cutoff frequency of 100 Hz in order to capture the diastolic blood flow. Subsequently, the blood flow waveform was visualized, using a velocity range of 100 cm/s and a sweep speed of 200 mm/s. The minimum measurable time period was 1 millisecond(4).

Doppler indices were measured 24 hours before delivery for all diabetic mothers admitted for delivery with GA 34-39 weeks.

Following delivery, the assessment of every neonate included the determination of Apgar scores at both the 1-minute and 5-minute marks, as well as the examination of the incidence of RDS and the need for NICU admissions. The diagnosis of neonatal RDS was made by pediatricians who were unaware of the fetal MPA Doppler waveform measurements. This diagnosis was based on the infant's clinical history, findings from the clinical examination related to respiratory compromise, increased oxygen consumption, response to surfactant therapy, and evidence of hyaline membrane disease observed in the chest radiograph. The diagnosis was confirmed in each instance by meticulous examination of the medical data.

The sample size was calculated at a confidence interval equal to 1.96, the standard deviation of pulmonary artery resistance index among neonates with respiratory distress in diabetic women as 0.249 (11), and an absolute error of 5%. After adding a dropout of 10%, the sample size was 103 patients.

Statistical analysis:

The data was analyzed using the statistical software SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The assessment of the normal distribution of variables was conducted using the Kolmogorov-Smirnov test. The data underwent statistical analysis, which included the calculation of metrics such as the mean and standard deviation. In addition, frequencies were calculated to represent the total number of instances, and percentages were generated when deemed suitable. The chi-square test was used to analyze categorical variables, whilst the t-test was utilized for continuous variables characterized by data that adheres to a normal distribution. The data was subjected to statistical analysis using multiple analysis of variance (ANOVA), using the Bonferroni adjustment for post hoc comparisons. In this study, linear regression analysis was used to examine the relationship between central pachymetry and the spherical equivalent (SE). The computation of the correlation coefficient (r) was performed in order to assess the strength and direction of the link. The Pearson correlation coefficient was computed in order to assess the association between the variables under investigation. In all of the aforementioned tests, the significance threshold was established at a 5% level by the use of a student t-test (t) and the corresponding probability (P value). A P value below the critical threshold of 0.05 is often seen as having statistical significance, whereas a P value beyond 0.05 indicates a lack of statistical significance.

Results:

This prospective study included 103 pregnant diabetic women, categorized into two groups; group (1) included 50 diabetic women with preterm labor (GA: 34 – 36+6 weeks), and group (2) included 53 women with full-term gestation (GA: 37 – 38.6 weeks).

Neonatal RDS affected 35/50 (70%) and 8/53 (15.1%) preterm and term infants, respectively. Both groups were matched in age, parity, and BMI, while the gestational age and fetal gender showed statistically significant differences **(Table 1).**

Table (1): Demographic characteristics of the studied groups

		Group (1), preterm (N = 50)		Group (2), full term (N = 53)		P value
		No RDS (15)	RDS (35)	No RDS (45)	RDS (8)	
Age (years) (Mean ± SD)		21.2 ± 1.69	27.7 ± 3.77	25.6 ± 4.15	28.9 ± 6.22	0.229[a]
GA at (weeks) (Mean ± SD)		35.5 ± 0.68	35.6 ± 0.81	37.9 ± 0.45	37.8 ± 0.56	0.048[a]
Fetal gender N (%)	**Males**	6 (40%)	16 (45.7%)	17 (37.8%)	4 (50%)	0.013[chi]
	Females	9 (60%)	19 (54.3%)	28 (62.2%)	4 (50%)	
Parity (Mean ± SD)		1.6 ± 1.26		1.49 ± 1.29		0.063[t]
BMI (kg/m^2) (Mean ± SD)		25.41 ± 3.06	27.25 ± 3.51	26.73 ± 3.54	26.53 ± 1.87	0.147[a]

GA: Gestational age, a: ANOVA test, chi: chi square test, t: student T test

Regarding obstetric outcomes, there was no variance among 2 groups in the mode of delivery ($p > 0.05$). Also, the gestational age at birth was significantly advanced in the term group rather than the preterm one (37.1 ± 2.41 versus 35.7 ± 2.41, respectively, p-value 0.025). Consequently, fetal birth weight and Apgar score significantly increased in the term group **(Table2).**

Table 2: Obstetric outcome of the studied population

		Group (1), preterm (N = 50)		Group (2), full term (N = 53)		P value
		No RDS (15)	RDS (35)	No RDS (45)	RDS (8)	
Mode of delivery N (%)	**NVD**	6 (40%)	18(51.4%)	22(48.9%)	6 (75%)	0.184[chi]
	CS	9 (60%)	17 (48.6%)	23 (51.1%)	2 (25%)	

GA at delivery (w) (Mean ± SD)	35.7 ± 2.41		37.1 ± 2.41		0.025[t]
Birth weight (kg) (Mean ± SD)	2343 ± 346.5	1697 ± 363.9	3147 ± 536.5	3488 ± 372.3	0.002[a]
Apgar score (Mean ± SD)	8.267 ± 0.704	5.571 ± 0.502	8.756 ± 0.857	5.625 ± 0.518	0.0001[a]

a: ANOVA test, chi: chi square test, t: student T test.

Ultrasonographic Doppler parameters demonstrated significant difference in AT, AT/ET, PSV, EDV, mean velocity and RI while ET, Pulsatility index demonstrated non-significant variance in comparison among 2 studied groups **(Table 3)**.

Table (3): Fetal MPA Doppler parameters of the two studied groups.

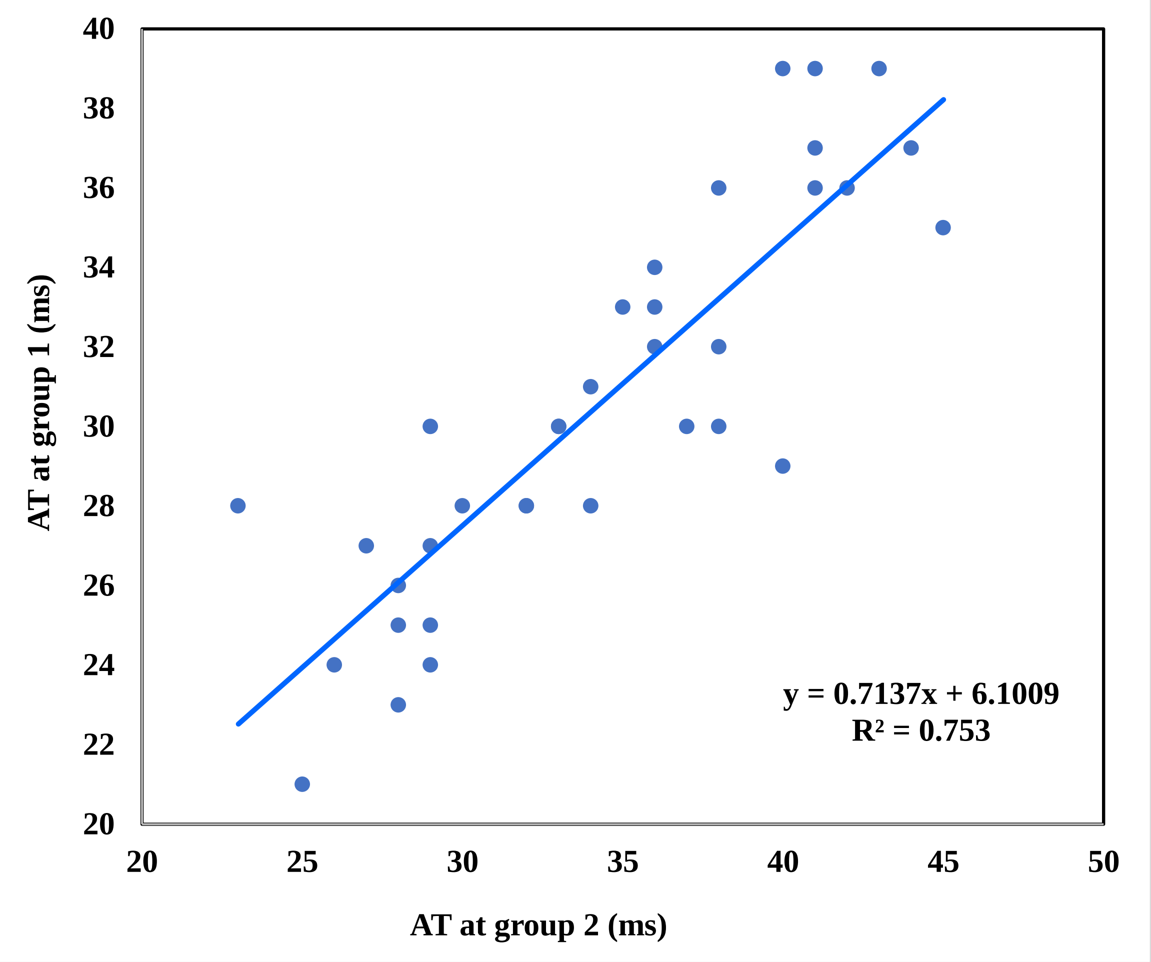
	Preterm	**Full term**	**t**	**P**
AT (s)	6.712 ± 3.23	9.008 ± 1.55	1.796	0.009*
ET (s)	22.23 ± 1.99	24.47 ± 1.66	0.384	0.137
AT/ET	0.277 ± 0.043	0.21 ± 0.06	0.957	0.045*
PSV (cm/s)	59.62 ± 12.29	69.63 ± 11.64	0.963	0.043*
EDV (cm/s)	7.943 ± 5.397	19.49 ± 6.73	8.356	0.000*
MV (cm/s)	17.62 ± 6.11	34.45 ± 5.23	6.527	0.000*
PI	2.232 ± 0.286	2.02 ± 0.361	0.324	0.172
RI	0.849 ± 0.136	0.717 ± 0.14	1.015	0.041*

t: student t-test, *P <0.01: highly significant, AT: Acceleration time, ET: Ejection time, PSV: Peak systolic velocity, EDV: End-diastolic velocity, MV: Mean velocity, PI: pulsatility index, RI: Resistive index.

Subgroup analysis revealed a significant difference in the Doppler parameters but for ET between preterm infants with and without RDS (p-value < 0.05). Also, ET, PSV, and MV showed no significant difference in term infants with and without RDS (p-value> 0.05).

The regression line demonstrated a highly significant positive correlation among RDS and AT in 2 groups (r= 0.8678, P = 0.0001) **(Figure 1).**

Figure 1: Correlation coefficient (r) of acceleration time (AT) of diabetic mothers' neonates with and without respiratory distress syndrome between the two groups.



Discussion:

The presence of maternal hyperglycemia is correlated with a heightened risk for newborn RDS.(12). It was rendered to preterm delivery, birth asphyxia, and metabolic derangement, leading to inadequate surfactant production (13). Great effort was directed to evaluating FLM using different means, including fetal biometry, placental maturity, umbilical artery Doppler studies, lung echogenicity, and ossification centers. Nevertheless, none of these studies exhibited the necessary level of reproducibility or reliability (10).

We recruited women with GA beyond 34 weeks. This was due to increased fetal lung immaturity before 34 weeks, making testing for FLM unimportant (14). RDS occurred significantly more in the preterm group than in the term. This would be related to poor glycemic control among those delivered preterm (15). Additionally, diabetes is associated with delayed production of phosphatidylglycerol, which is paramount for surfactant production (16).

In the current study, ultrasonographic Doppler parameters show statistically significant differences (p <0.01) in AT, AT/ET, PSV, and mean velocity. In contrast, ET, EDV, Pulsatility index, and Resistive index demonstrated non-significant differences compared to 2 studied groups. This was following ***Moety et al. (10)***, who had the same results but with higher PI and RI in the NRDS group and added that Fetuses that exhibit RDS have elevated levels of pulmonary vascular resistance and pressure, as well as reduced pulmonary blood flow, in comparison to fetuses unaffected by RDS. Additional studies reported lower MPA At/Et in preterm fetuses that developed RDS (4, 5). Different PI results between results would be rendered to different pulmonary vasculature as pregnancy advances (4). Other studies reported an increased AT/ET ratio in mature lungs than in immature ones, which agreed with the current results (3, 10).

Doppler studies revealed a strong positive association with RDS development in the entire population. This agreed with previous results where AT and AT/ET ratio predicted neonatal RDS significantly (4). Contradicting results reported an insignificant AT/ET ratio value in the prediction of neonatal RDS. However, this study recruited a small sample size with only one fetus diagnosed with RDS (8).

Strength and limitations:
The present investigation was carried out using a prospective research strategy. The Doppler measurements were acquired on the day of delivery, therefore mitigating any potential fluctuations in the recorded values. The practical implications of this study are heightened due to the inclusion of a diverse cohort with a range of comorbidities. Several limitations were identified, such as the relatively limited sample size, which might potentially affect the accuracy of the data and the statistical analysis. A control group consisting of women without diabetes was not included in the study. Additional research is required to ascertain if MPA At/Et has the ability to forecast the occurrence of infant RDS in women who are not in labor and those who are scheduled for elective CS, despite the current study's results indicating its predictive capability for women in labor and those who are advised to have selective CS.

Conclusion: The major pulmonary artery in the fetus, the incidence of infant RDS was predicted by Doppler scans.

Conflict of interest: None

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