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Combined Fetal Pulmonary Artery Doppler and Proximal Humeral Ossification Center for Prediction of Neonatal Respiratory Distress Syndrome at Term: A Cohort Prospective Study

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Abstract

Background: Fetal lung maturity is one of the huge dilemmas since a long time ago. The delivery time is crucial for safe fetal delivery since verification of pulmonary maturity diminishes the respiratory morbidity possibility. Recently Pulmonary artery indices have been used to predict the possibility of respiratory distress syndrome (RDS) especially in early term. Together with humeral ossification center which has a remarkable value in estimation of term gestation, both of them can help prediction of fetal lung maturity.

Aim: Utilizing PHE with pulmonary artery Doppler indices for accurate prediction of fetal RDS. The use of PHE in prediction of term gestation.

Patients and methods: This study included 115 uncomplicated singleton pregnant women with gestational age between 37 and 40 weeks patients from Al-Azhar University Ob/Gyn Hospitals during the period from November 2019 to October 2020. The ultrasound scans were done within 24 h interval before delivery with Cesarean section. After delivery, the neonatal Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 1, 5 min, fetal diagnosis with RDS, any NICU admission were recorded, respectively.

Results: Pulmonary artery resistive index (RI) and PHE had statistically significant diagnostic performance in predicting fetal distress. PHE of less than or equal to 1.95 had highest diagnostic characteristics in predicting fetal distress. Among Pulmonary Artery Doppler, RI of greater than or equal to 0.79 had highest diagnostic characteristics.

Conclusion: PHE and Pulmonary artery R.I could predict fetal distress. Pulmonary artery indices and PHE combination (sum) predicted fetal distress better than using pulmonary indices alone. Presence of PHE confirms term gestation.

Keywords: Pulmonary artery resistive index, Proximal Humeral Epiphysis (PHE), Neonatal respiratory distress syndrome

1. Introduction

Early-term delivery is justified occasionally due to several medical or obstetric conditions. Weighing newborn and maternal hazards resulting from earlier delivery against hazards due to continuation of gestation would specify the optimal time for parturition. It is not recommended to delay delivery to the 39 week of pregnancy in the presence of maternal or fetal conditions requiring earlier parturition.¹

Neonatal respiratory distress syndrome (NRDS) is a breathing condition occurring immediately at, or soon after birth (<24 h), NRDS severity rises during the first two days after delivery.²

NRDS results from deficiency of pulmonary surfactant compromising alveolar integrity, hindering gaseous exchange owing to unregulated surface tension of lung acini.³ NRDS advances through several stages as hypoventilation, hypoxemia and respiratory acidosis.⁴ The incidence of RDS among

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full term neonates was 1.64.⁵ NRDS is the most prominent reason for NICU admission with an incidence of 7.8% as well as death risk reaching 50% among premature infants.⁶

Evaluation of the chest maturity can be a really challenging in the absence of an optimum scheme to confirm neonatal lung maturity. A few invasive prenatal techniques such as; Lecithin/sphingomyelin ratio, phosphatidylglycerol testing and others have been involved in assessing pulmonary maturity. However, none of them proved to be superior over the rest according to controlled studies.⁷

Nevertheless, amniocentesis is an invasive procedure recommended for specific indications, and this test has high sensitivity but only moderate specificity,⁸ so it is an additional cause for pregnant ladies to avoid them.

Doppler parameters of fetal Main Pulmonary Artery (MPA) can indirectly reflect changes pulmonary vascular force; consequently it can forecast NRDS indirectly since surfactant inadequacy results in elevated pulmonary impedance with an increase in artery pressure.⁷ When fetal lungs grow during gestation, so does the pulmonary vasculature, where there is an increase in number of pulmonary arteries and amount of smooth muscular tissue resulting in lower pulmonary arterial vascular resistance, leading to a gradual increase in pulmonary blood flow.⁹

Expected Date of Delivery (EDD) calculation guides the entire decision making in obstetrics. Traditionally, last menstrual period calculates the EDD.¹⁰ Some noninvasive ultrasound markers, as the transverse cerebellar diameter and finding of specific ossification centers were suggested for assessing gestational age during last trimester of pregnancy.¹⁰

Pulmonary maturity of fetus can depend on finding specific sonographic markers suggesting that a fetal gestation has reached its last trimester. These markers included the distal femoral, proximal tibial and proximal humeral epiphyseal ossification centers.¹¹ The PTE correlated with the 37th week of gestation with a high Positive Predictive Value, similarly the PHE suggested 38th week of pregnancy with excellent positive predictive value.¹¹

In our study we aimed to assess of fetal pulmonary artery Doppler and PHE for precise prediction of NRDS. Also, using the PHE in correlation with gestational age to indicate this is a term fetus.

2. Patients and methods

115 pregnant women joined from Al-Azhar University obstetrics and gynecology hospitals during the

period from November 2019 to October 2020. Our Inclusion criteria were uncomplicated singleton pregnant women with the following criteria: age of the patient between 18 and 40 years old, Gestational age from 37 to 40 weeks with accurate gestational age dating (dating by last menstrual period and confirmed by first trimesteric ultrasound) and delivered within 24 h of ultrasound. Our study approval was obtained by the hospital research ethics committee.

While we excluded those who had an age below 18 or above 40, who had fetal chromosomal or structural abnormality, fetal growth less than tenth or greater than the 90th percentile for gestational age, any maternal pregnancy complication, placenta previa or morbid adherent placenta, Multiple pregnancy, those with admission to delivery time exceeding 24 h and those who received antenatal corticosteroids.

All patients in our study were subjected to the following: a formal consent was obtained; detailed history was taken in form of name, age, marital status, obstetric code, menstrual history, past history, family history, occupation, address, history of drug intake, contraceptive methods, any systemic disease, and previous investigations and treatment. For precise gestational age calculation (dating by a certain last menstrual period or by first trimesteric ultrasound). Thorough general and pelvic examination: vital signs, height, weight and BMI to exclude medical disorders and obstetric palpation (Maneuvers of Leopold) were done. Obstetric Ultrasonography was done including the participants laying in the supine position on a mattress. A coupling gel was applied to the pelvic probe. A single examiner (from the authors' team) performed all ultrasound examinations using the Voluson E6 ultrasound machine (GE Healthcare Austria GmbH, Seoul, South Korea) equipped with a convex transducer 3–5 MHz in frequency. A routine ultrasound examination, including fetal biometric measurements, expected fetal weight and amniotic fluid index were done. Axial view of fetal thorax was obtained, while the fetus is at rest without fetal breathing motion, the sonographer followed the Main pulmonary artery till halfway between the pulmonary valve and the division to right and left branches. Sample gate of pulsed Doppler was adjusted to 3 mm and the isonation angle was sustained at $\approx 15^\circ$. For the finest velocity waveform display, Doppler gain and scale were attuned to display the peak systolic velocity (PSV) and early diastolic notch. The MPA Doppler waveform appeared where it has a distinctive appearance (sharp systolic peak blood flow with a needle-like appearance). A reversed flow little notch of was observed at the end of the systole (Fig. 1). After

acquiring the ideal main pulmonary artery waveform, related Doppler indices were manually traced three times and the average was taken. The indices included the (S/D) ratio, Pulsatility index (PI), (RI) and the PSV (Fig. 2).

PHE identification by sonography was done using real-time B- mode equipment with 3.5 MHz convex transducer via ultrasound device (E6, Voluson). PHE of the fetus was recognized by adjusting the transducer in the larger direction of humeral axis and was perceived to exist if a one, central, well-defined echogenic focus was detected near the humeral head. Two operatives examined the images. In presence of any disagreement, mutual agreement was obtained as present or absent PHE.

Diagnosis of NRDS after delivery: the delivery method was recorded. A single blinded pediatrician to the fetal MPA vascular indices handled the neonate. Fetal birth weights as well as Apgar scores (at 1 and 5 min) were documented. NRDS diagnosis relied on presence of clinical features of RDS (tachypnea, retractions and/or nasal flaring), supplemental oxygen need of 0.4 or more for a minimum of 24 h and classic chest radiography displaying reticulogranular patterns, air bronchograms and ground glass appearance.

2.1. Statistical analysis

The required sample size has been calculated using the G*Power Software (Universität Düsseldorf, Germany).

2.2. Statistical methods

The gathered data were tabulated, coded and statistically analyzed using IBM SPSS statistics

(Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data tested for normality using Shapiro–Wilk test, then described as mean \pm SD (standard deviation) as well as maximum and minimum of the range, then compared using independent t-test (two independent groups) and ANOVA test (three independent groups). Qualitative data described as number and percentage and compared using Fisher's Exact test for variables with small expected numbers. Linear regression model was used to discover independent factors predicting gestational age. ROC curve was utilized to assess the performance of different tests to distinguish fetal distress. The level of significance was taken at *P*-value less than 0.050 was significant, otherwise was non-significant.

3. Results

115 uncomplicated singleton pregnant women with gestational age between 37 and 40 weeks pregnant women enrolled in this study. Nearly 10% of the delivered fetuses developed RDS and were admitted to the NICU (Table 1). shows that there was a statistically significant lower APGAR score at 1 and 5 min among the RDS group. The table also showed Absent statistically considerable difference according to respiratory distress regarding maternal age, body mass index and parity as well as fetal gestational age and weight. No statistical significant difference according to respiratory distress regarding indication of current cesarean section.

Table 2 shows that: Ossification center and PSV statistically were significantly lower in cases with respiratory distress. PI and S/D ratio statistically were nonsignificantly higher in cases with respiratory

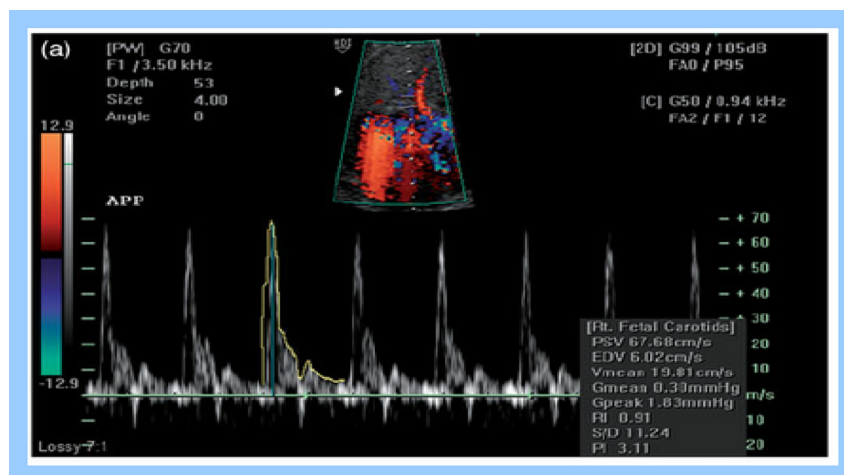


Fig. 1. Proximal segment of the fetal pulmonary artery detected by color and pulsed Doppler.¹²

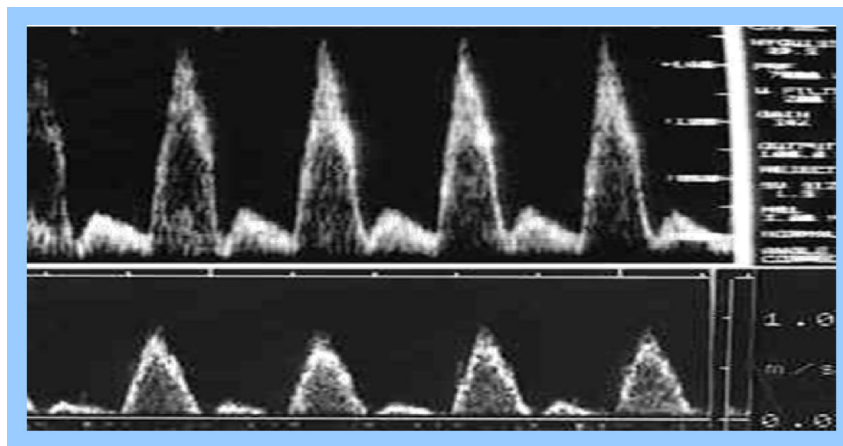


Fig. 2. Doppler waveforms of Ductus Arteriosus.¹³

distress. RI statistically was significantly higher in cases with respiratory distress (Fig. 3). Pulmonary Artery Doppler and Proximal Humeral Ossification center combination (sum) statistically was significantly lower in cases with respiratory distress.

Table 3 shows that: Pulmonary Artery Doppler findings; Mean \pm SD of PI, RI, S/D ratio and PSV were 2.07 ± 0.67 , 0.76 ± 0.05 , 6.88 ± 0.33 and 50.45 ± 7.48 , respectively. While Proximal Humeral Ossification center Mean \pm SD was 3.42 ± 1.93 mm. Combining Pulmonary Artery Doppler and Proximal Humeral Ossification center by summation Mean \pm SD was 63.58 ± 7.93 . Only Proximal Humeral Ossification center showed statistical

significant elevation of its means across the studied gestational age (Fig. 4).

Table 4 shows that: Ossification center statistically had significant high diagnostic performance in predicting fetal distress. RI statistically had a significantly lower diagnostic ability in estimating fetal distress. PI and S/D ratio statistically had non-significant diagnostic performance in predicting fetal distress. Pulmonary artery PSV and Pulmonary Artery Doppler R.I and Proximal Humeral Ossification center combination (sum) statistically significant moderate diagnostic performance in predicting fetal distress, higher than those of Pulmonary artery PSV and R.I but lower than Ossification center alone (Fig. 5).

Table 1. Comparison according to respiratory distress regarding maternal and fetal demographic characteristics.

Variables	Respiratory distress (N = 12)	No respiratory distress (N = 103)	P-value
Age (years)	28.9 \pm 2.6	28.2 \pm 3.1	$\hat{>}$ 0.455
BMI (kg/m ²)	29.0 \pm 2.0	28.6 \pm 2.7	$\hat{>}$ 0.626
GA (weeks)	38.5 \pm 0.7	38.8 \pm 0.6	$\hat{>}$ 0.068
Fetal weight (kg)	3.125 \pm 0.136	3.193 \pm 0.197	$\hat{>}$ 0.249
Parity			
Nulliparous	3 (25.0%)	33 (32.0%)	\S 0.751
Parous	9 (75.0%)	70 (68.0%)	
Indication of current cesarean section			
Repeated cesarean section	6 (50.0%)	57 (55.3%)	\S 0.631
Rupture of membranes	3 (25.0%)	30 (29.1%)	
Decreased fetal kicks	1 (8.3%)	7 (6.8%)	
abnormal fetal heart tracing	1 (8.3%)	5 (4.9%)	
Malpresentation	1 (8.3%)	4 (3.9%)	
Birth weight (kg)	3.083 \pm 0.164	3.189 \pm 0.195	$\hat{>}$ 0.074
APGAR-1	4.6 \pm 0.8	6.5 \pm 0.5	$\hat{>}$ <0.001*
APGAR-5	4.9 \pm 1.1	7.7 \pm 0.8	$\hat{>}$ <0.001*

Bold indicates that the result is statistically significant unlike all other results in the table.

4. Discussion

Fetal lung maturity is one of the huge dilemmas since a long time ago. It's an important reason to consider when delivering the fetus safely where the confirmation of mature fetal lungs, decreases the possibility of chest morbidity. Thus verification of pulmonary maturity is a known exemption to old

Table 2. Pulmonary Artery Doppler and Proximal Humeral Ossification center among the studied cases.

Variables	Respiratory distress (N = 12)	No respiratory distress (N = 103)	P-value
Ossification center (mm)	1.58 \pm 1.99	3.63 \pm 1.81	$\hat{>}$ <0.001*
Pulmonary artery PI	2.15 \pm 0.74	2.06 \pm 0.66	$\hat{>}$ 0.655
Pulmonary artery RI	0.79 \pm 0.05	0.75 \pm 0.05	$\hat{>}$ 0.002*
Pulmonary artery S/D ratio	6.97 \pm 0.80	6.87 \pm 0.22	$\hat{>}$ 0.685
PSV	44.68 \pm 8.60	51.12 \pm 7.08	$\hat{>}$ 0.004*
Combination (sum)	56.26 \pm 9.46	64.44 \pm 7.32	$\hat{>}$ <0.001*

Bold indicates that the result is statistically significant unlike all other results in the table.

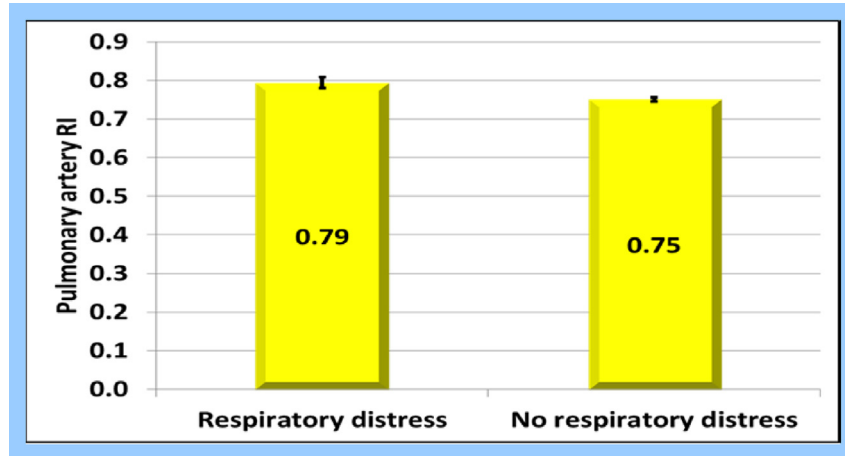


Fig. 3. Comparison according to respiratory distress regarding Pulmonary Artery Doppler RI.

recommendations conflicting with elective C.S before 39th week in pregnancy Bates and colleagues.¹⁴

RDS is an unfavorable outcome and is one of the highest if not the highest cause of NICU admission and neonatal mortality.¹⁴ Another study by Condò and colleagues¹⁵ has shown that RDS, had a small risk later in pregnancy, with an incidence of nearly 3% at 36th weeks, 1.5% at 37th weeks and 0.5% at 38th week.

Previously the biochemical methods of assessment of fetal lung maturity were the benchmark after the detection of the L/S ratio by Gluck and colleagues¹⁶ The cut-off L/S ratio of 2 indicated a less likely RDS Field and colleagues.¹⁷ Other tests included measurement of phosphatidylglycerol Garite and colleagues.¹⁸ Phosphatidylglycerol rises markedly in fetal liquor by certain duration after the lecithin rise Towers and Garite.¹⁹

Amniocentesis is trustworthy method for neonatal lung maturation assessment and can be done until 37th weeks in pregnancy. However it has some

shortcomings for instance; Preterm Prelabor Rupture of Membranes (PPROM) chorioamnionitis, abruption placenta and fetomaternal hemorrhage Ahmed and colleagues.²⁰ Amniocentesis was performed vastly in that era where fetal imaging new technology was not existing back then Varner and colleagues.²¹

Placental grade and biparietal diameter (BPD) sonographic evaluation were performed, where lung maturation is expected to be found in the presence of high grade placenta and BPD crossing 9 cm. However it didn't turn out to be reliable due high false positive results Hadlock and colleagues.²² Other markers in form of, comparing lung echoes to the liver echo Sohn and colleagues²³ or presence of free floating particles in amniotic fluid were also used back then Hallak and colleagues.²⁴

Recently, fetal pulmonary artery Doppler velocimetry has been proven to be a trustworthy noninvasive technique in assessing maturity of chest of the fetus, analogous to the manner in which MCA

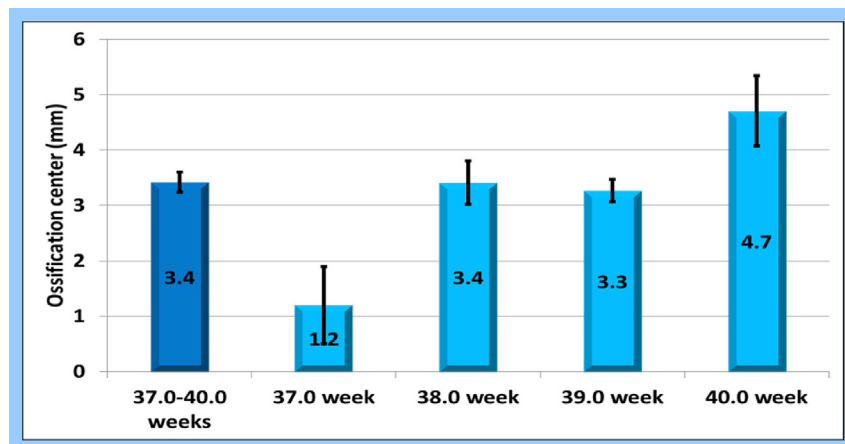


Fig. 4. PHE among the studied cases.

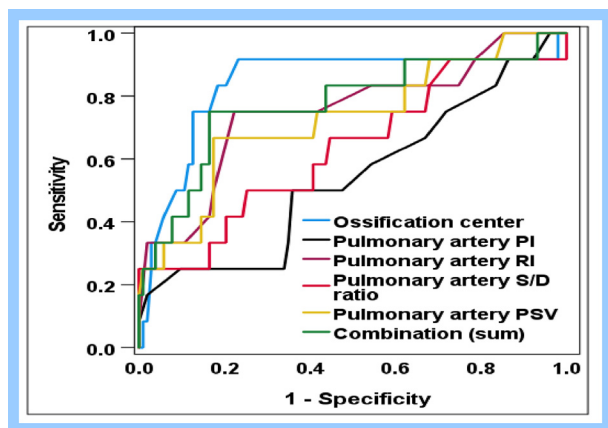


Fig. 5. ROC curve for Pulmonary Artery Doppler and PHE in predicting fetal distress.

has substituted amniocentesis in evaluating anemia in the fetus Kim and colleagues.²⁵ Fetal main pulmonary artery Doppler waveform offers a non-interventional method to forecast neonatal lung maturation with high accuracy Schenone and colleagues.²⁶ In addition fetal pulmonary artery indices as Pulsatility Index, Resistance Index and Acceleration time/Ejection time proved that they can anticipate NRDS and can evaluate pulmonary maturation being precise non interventional techniques Aboulghar and colleagues.²⁷

In the current study we measured the pulmonary artery indices such as R.I, P.I, PSV and S-D ratio combined with PHE for Prediction of RDS at term delivery by Cesarean section. Then we compared these data from two groups, the first of fetuses who developed RDS and the second fetuses who did not.

We have found that RDS fetuses compared with those who did not had the following findings of significantly higher R.I with cut off value of (≥ 0.79) having a sensitivity and specificity of (75.0%,77.7%) respectively. On the contrary the PSV was significantly lower with cut off value of less than or equal to 46.3 with a sensitivity of 66.7% and a specificity of 82.5%. Similarly the PHE was significantly lower in the RDS group with cut off value of 1.58 ± 1.99 compared with 3.63 ± 1.81 in Non RDS group with a P-value of $<0.001^*$.

A new parameter in this study was Combination (sum) of pulmonary artery indices including (P.I, R.I, PSV, S/D ratio) to the PHE to predict RDS. This combined parameter showed a cut off value of less than or equal to 58.17 in RDS group with AUC 0.775, SE 0.083, P-value 0.002*, 95% CI 0.612–0.937. Furthermore this combined parameter had significant smaller results in respiratory distress group in comparison to the other group.

Ossification center statistically had significant high diagnostic performance in predicting fetal distress. PI and S/D ratio statistically had nonsignificant diagnostic performance in predicting fetal distress. RI statistically had significant low diagnostic performance in predicting fetal distress. Pulmonary artery PSV and Pulmonary Artery Doppler and PHE combination (sum) statistically significant high diagnostic performance in predicting fetal distress, but lower than Ossification center alone.

In a recent study by Khalifa and colleagues,²⁸ RDS fetuses had a significantly higher MPA RI which is equivalent to our findings. Yet they had a significantly higher MPA P.I which differed from ours.

Table 3. Pulmonary Artery Doppler and Proximal Humeral Ossification center among the studied cases.

Variables	Measures	All cases (N = 115)	Week-37 (N = 2)	Week-38 (N = 31)	Week-39 (N = 70)	Week-40 (N = 12)
Ossification center (mm)	Mean \pm SD	3.4 ± 1.9	1.2 ± 1.0	3.4 ± 2.2	3.3 ± 1.7	4.7 ± 2.2
	Range	0.1–7.9	0.5–1.9	0.1–7.7	0.2–6.5	1.2–7.9
	\hat{P} -value	0.038*				
PI	Mean \pm SD	2.1 ± 0.7	2.0 ± 0.5	2.0 ± 0.6	2.1 ± 0.7	2.2 ± 0.8
	Range	1.1–3.3	1.6–2.3	1.1–3.2	1.1–3.3	1.3–3.1
	\hat{P} -value	0.837				
RI	Mean \pm SD	0.8 ± 0.0	0.8 ± 0.0	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.0
	Range	0.6–0.9	0.8–0.8	0.6–0.8	0.6–0.9	0.7–0.8
	\hat{P} -value	0.339				
S/D ratio	Mean \pm SD	6.9 ± 0.3	7.4 ± 0.8	6.9 ± 0.2	6.9 ± 0.4	6.9 ± 0.2
	Range	4.8–8.0	6.8–8.0	6.4–7.3	4.8–8.0	6.5–7.1
	\hat{P} -value	0.145				
PSV	Mean \pm SD	50.4 ± 7.5	45.2 ± 19.9	50.9 ± 6.6	50.1 ± 8.0	52.0 ± 4.0
	Range	31.1–65.5	31.1–59.2	36.2–65.5	32.9–65.3	47.9–60.0
	\hat{P} -value	0.630				
Combination (sum)	Mean \pm SD	63.6 ± 7.9	59.4 ± 23.7	63.7 ± 6.5	63.1 ± 8.5	66.5 ± 4.7
	Range	42.7–81.4	42.7–76.2	46.6–75.9	44.9–81.4	60.5–76.3
	\hat{P} -value	0.507				

Table 4. Diagnostic performance of Pulmonary Artery Doppler and Proximal Humeral Ossification center in predicting fetal distress.

Variables	AUC	SE	P-value	95% CI	Cut point
Ossification center	0.838	0.076	<0.001*	0.689–0.987	≤1.95
Pulmonary artery PI	0.542	0.094	0.638	0.357–0.727	≥2.25
Pulmonary artery RI	0.749	0.083	0.005*	0.588–0.912	≥0.79
Pulmonary artery S/D ratio	0.631	0.093	0.140	0.449–0.813	≥6.99
Pulmonary artery PSV	0.726	0.084	0.011*	0.561–0.891	≤46.35
Combination (sum)	0.775	0.083	0.002*	0.612–0.937	≤58.17

Bold indicates that the result is statistically significant unlike all other results in the table.

This variation in data could be attributed to earlier gestational age included in the study and the use of three dimensional ultrasound in that study.

Likewise, another recent study by Kandil and colleagues²⁹ found that the MPA RI was significantly higher in fetuses that developed RDS. Another finding was the fetal tibial epiphysis was a good indicator of lung maturity. In our study we measured the PHE center which was significantly lower in the RDS group which is relatively similar to their study, but their study included preterm and they did not combine two parameters together, they used each alone.

Identically Laban and colleagues³⁰ identified mean Pulmonary Artery R.I as reliable predictor of neonatal RDS at term which is similar to our findings. Furthermore, they differed from our study in combining the fetal lung volume while we used PHE. Both studies showed that combining two measures had a greater predictive value than when using pulmonary artery R.I measure alone.

Compatible with Pouya and colleagues³¹ study, PSV was significantly lower in RDS group of fetuses. Still, their study showed no significance as regards RI, PI values between the two groups.

Consistent with our results Moety and colleagues³² proved that RDS fetuses had significantly elevated PI and RI with decreased PSV. All the previously mentioned indicate that lesser pulmonary blood flow and greater pulmonary vascular resistance are found in RDS fetu when in comparison to the other group negative for RDS. However the difference was that we found that the sum of ossification center and Doppler indices improved the diagnostic accuracy of RDS. This may be correlated that Moety and colleagues³² had a larger number of cases including fetuses born preterm and at term therefore the ability to prove that Doppler indices could change with advancement of gestational age.

In contrary to our results Kim and colleagues²⁵ showed no significance in pulmonary artery R.I and P.I in RDS fetuses compared with those who did not which may be explained by preterm study subjects.

According to Shin and colleagues³³ the incidence of RDS decreases with advancing gestational age and the ossification centers were valuable indicator of gestational age. Therefore using ossification centers for prediction of RDS was justified.

The PHE starts to appear at a gestational age of 36 weeks and is more frequently present and visible with progress of the gestational age based on Garg and colleagues¹² study. PHE can be used as a good predictor of term gestation, since their study displayed high specificity, Positive Predictive Value and sensitivity values after crossing 38 weeks of gestational age.

Another study by Delle Donne and colleagues,³⁴ showed that the presence of PHE at a gestational age of greater than or equal to 38 weeks with a sensitivity and specificity 91% 89% and 40% 100% respectively.

Abd EL-Fattah and colleagues³⁵ found a highly significant presence of PHE in (89.8%) who did not develop RDS and those with RDS had an absent PHE in all cases. These data are consistent with our data in that PHE is significantly present in fetuses without RDS so its presence is an important predictor of lung maturity and that RDS has a very low risk if baby was to be delivered.

Humeral epiphyseal ossification center predicted respiratory distress with cut off value of 3.0 Sefi Elnasr and colleagues³⁶ Similarly the presence of PHE was significantly higher in Non RDS group, where the PHE appears after 36 weeks of gestation and possibility of respiratory distress is lower as gestational age increases. This above data indicates that the PHE grows faster when in comparison to the other ossification centers at term Awad Amin Abd El-Hady and colleagues.³⁷

4.1. Conclusion

We can conclude that PHE and pulmonary artery Doppler indices are valuable Noninvasive markers which can be used separately or together for reliable prediction of RDS at term infants. Moreover, PHE serves as an accurate predictor of RDS at term fetuses since it appears when the fetus is mature

indicating term gestation and concurrently the fetal lung is mature too.

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Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

Authors declared there was no conflict of interest.

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