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Evaluation of thalamus echogenicity via ultrasonography as a marker of fetal lung maturity

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Abstract
Background: Fetal lung immaturity is a major problem in the management of elective birth with respect to predicting the development of infant respiratory distress syndrome (IRDS) in the neonate after birth.
Aim and Objectives: The aim of this study was to evaluate the validity of measuring fetal thalamic echogenicity by ultrasound as a marker of fetal lung maturity.
Subjects and Methods: This was a prospective observational study that was being carried out on 80 pregnant patients. They were recruited from Obstetrics and Gynaecology clinics at Tanta University Hospitals during the period of research from March 2021 till the end of the study.
Results: There was statistically significant difference between RDS group and those without RDS regarding thalamic echogenicity, 1 and 5- min APGAR score, NICU admission and neonatal mortality.
Conclusion: Evaluation of echogenic thalamus by ultrasound at the level of the BPD is of value, and can be considered as a new marker of fetal lung maturity; however, further studies are required to strengthen such idea.

Keywords: Fetal lung maturity, thalamic echogenicity, ultrasound

Introduction
Most babies have mature lungs by 37 weeks of gestation. However, since babies develop at different rates, there are exceptions to this. The risk of complications increases the earlier the baby is born with increased risk of Respiratory Distress Syndrome (RDS) [1].
Moreover, approximately 11% of all infants are born preterm, with this figure rising in many countries internationally [2].
Respiratory pathology is one of the commonest consequences of preterm birth manifesting early as respiratory distress syndrome (RDS), a product of structurally immature lungs and pulmonary surfactant deficiency. These preterm infants often require invasive and non-invasive respiratory support, supplementary oxygen and surfactant replacement therapy. A proportion of these infants will go on to develop chronic lung disease of prematurity, with abnormal respiratory function and increased respiratory morbidity persisting through childhood and into adult life [3].
Neonatal Respiratory Morbidity (NRM) is the leading cause of mortality and morbidity associated with prematurity. Neonatal Respiratory Morbidity can be assessed through Fetal Lung Maturity (FLM) estimation, helping to decide on the use of corticosteroids or plan place and time of elective delivery. Traditional clinical options for fetal lung maturity estimation are either to use gestational age directly as a fetal lung maturity estimator or studying several components of the amniotic fluid through amniocentesis [4].
Assessment of fetal lung maturity for the prediction of neonatal respiratory morbidity may be relevant, particularly after 34 weeks of gestation, when the risk of neonatal respiratory morbidity ranges from 5% to 20%, to better assess the risk / benefit ratio of elective delivery and / or with the use of corticoisteroids [5].
Fetal lung maturity (FLM) is determined mainly by pulmonary surfactant and it can only be assessed with laboratory tests on amniotic fluid. The need for amniocentesis has resulted in a decline in the use of this information clinically. The non-invasive prediction of fetal lung maturity by fetal lung ultrasound images has been attempted for a quarter of a century by means of gray-level measurements, lung tissue motion and relative features of lung-to-placenta or -liver images, among others. These studies revealed a good correlation with respiratory morbidity, but the diagnostic accuracy was inadequate for clinical use [6].

The lecithin/sphingomyelin (L/S) ratio and the lamellar body count (LBC) are two invasive tests used to assess fetal lung maturity in pregnancies at risk for preterm delivery. Many studies have reported on the accuracy of this tests [7].

In an attempt to establish further non-invasive method for evaluation of fetal lung maturity, some studies reported that the fetal thalamus showed significant changes of echogenicity late in pregnancy which may have a place in assessing fetal lung maturity [8, 9].

Aim of this study is to evaluate the validity of measuring fetal thalamic echogenicity by ultrasound as a marker of fetal lung maturity.

This study will be prospective observational study that will be carried out on 80 pregnant patients. They will be recruited from Obstetrics and Gynaecology clinics at Tanta University Hospitals during the period of research from March 2021 till the end of the study.

Patients and Methods

This study will be prospective observational study that will be carried out on 80 pregnant patients. They will be recruited from Obstetrics and Gynaecology clinics at Tanta University Hospitals during the period of research from March 2021 till the end of the study.

Patients: Patients will be included according to inclusion and exclusion criteria.

Inclusion criteria

- Single living pregnancy,
- Uncomplicated pregnancy (No hypertension or diabetes),
- Normal amount of liquor approved by ultrasound.
- Patients admitted for elective cesarian section at 38 weeks of gestation will be assessed for thalamus echogenicity twice at 34 and 37 weeks of gestation calculated from the first day of LMP or by U/S examination before 14 weeks.

Exclusion criteria

1. Pregnant women who will refuse to participate.
2. Multiple pregnancies.
3. Fetal congenital anomalies.
4. Complicated pregnancy (hypertension, diabetes. etc…),
5. Oligohydramnios or polyhydramnios.
6. Intrauterine growth restriction or macrosomic fetuses.

Methods

The eligible subjects included in this study will be subjected to the following:

1. History taking: personal history, obstetrics history, past history of medication and surgeries, menstrual history, surgical history, and history of the current pregnancy.
2. General examination.
3. Abdominal ultrasonographic examinations will be performed by one investigator using a 3.5- 5-MHz transabdominal probe for 2D volume scanning and assessment of:
   - Fetal biometry (FL, AC, BPD),
   - Presentation,
   - Amniotic fluid index.
   - The amniotic fluid particles (vernix) and the placental changes will be also measured as a part of fetal wellbeing assessment
   - Thalamus echogenicity assessment:

During ultrasound examination we will look for the biparietal diameter (Transthalamic plane) which will be measured in millimeters, and the state of echogenicity of the thalamus will be recorded as echogenic or echolucent in comparison with the brain tissue between the thalamus and the parietal bone which is echogenic throughout pregnancy; if the echogenicity of the thalamus will appears like brain tissue, it will be considered echogenic, while if it will appear without echoes inside the thalamus it is echolucent. Thalamic echogenicity will be assessed twice at 34 and 37 weeks of gestation

Besides, the following criteria that predict fetal lung maturity also will be assessed:

- Placental changes according to the Grannunm classification,
- BPD which will be measured in millimeters,
- Vernix in the amniotic fluid.

After delivery

Each neonate will be examined for the following fetal outcomes: Fetal sex, weight, (APGAR score) at one and five minutes, signs of a respiratory problem, admission to the neonatal intensive care unit (NICU) and followed by the duration of hospitalization, and any adverse neonatal morbidity or mortality up to discharge

Statistical analysis: SPSS statistics for windows (Statistical Package for the Social Sciences) version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. One-way ANOVA with Bonferroni post hoc analysis and Kruskal Wallis with Dunn's post hoc analysis tests were used for inter-group comparison of parametric and non-parametric continuous data respectively. Categorical Group differences with Fisher exact and Chi square tests were used for inter-group comparison of nominal data. Bivariate Correlations were assessed using Pearson's or Spearman's correlation coefficient depending on the nature of data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

Results:

Table 1: Basic maternal characteristics among the participants

Variable		N= 80
Age (years)	Mean ± SD	32.7±5.6
	Median (34)	34 (22-40)
BMI (Kg/m^2)	Mean ± SD	23.1±1.9
	Median (23)	23 (20-26)

The mean age was 32.7±5.6 years among the participants. The age ranin from 22 to 40 years with median 34 years. The mean BMI was 23.1±1.9 among the participants. The BMI was ranging from 20 to 26 with median 23 (Table 1,).

Table 2: Obstetric history among the participants

Variable	N= 80
Primigravida, n (%)	20 (25)
Nullipara, n (%)	16 (20)
Previous abortion, n (%)	26 (32.5)
Previous caesarean, n (%)	27 (33.8)

There were 25% primigravida among the participants. There was 20% nullipara among the participants. There were 32.5% had previous history of abortion among the participants. There were 33.8% had previous history of caesarean among the participants (Table 2).

Table 3: Vital signs among the participants

Variable	Mean ± SD
Systolic blood pressure (mmHg)	119.8±12.3
Diastolic blood pressure (mmHg)	71.1±6.0
Pulse (b/m)	85.2±9.4
Temperature (c°)	37.6±0.4

The mean of systolic blood pressure was 119.8±12.3 among the participants. The mean of diastolic blood pressure was 71.1±6.0 among the participants. The mean of pulse 85.2±9.4 among the participants. The mean of temperature was 37.6±0.4 among the participants (Table 3).

Table 4: Transabdominal ultrasonography fetal parameters at 34 weeks among the participants

Variable	Mean ± SD
Gestational age (by LMP)	34.6±0.4
Biparietal diameter (mm)	77.6±12.8
Femur length (mm)	62.5±6.8
Abd. Circumference (mm)	294.6±20.6
Head circumference (mm)	270±2.1

The mean gestational age was 34.6±0.4 weeks among the participants. The mean BPD was 77.6±12.8 among the participants. The mean femur length was 62.5±6.8 among the participants. The mean abdominal circumference was 294.6±20.6 among the participants. The mean head circumference was 270±2.1 among the participants (Table 4)

Table 5: Transabdominal ultrasound finding at 34 weeks between the participants

Variable	n= 80
Amniotic fluid vernix	
Yes, n (%)	71 (88.8)
No, n (%)	9 (11.2)
AFI, Mean ± SD	130.7±7.3
Turbidity, n (%)	11 (13.8)
Placental calcification	
Grade I, n (%)	12 (15)
Grade II, n (%)	23 (28.7)
Grade III, n (%)	45 (56.3)

There were 88.8% had amniotic fluid vernix and 11.2% had no amniotic fluid vernix among the participants. The mean AFI was 130.7±7.3 among the participants. There were 13.8% had turbid amniotic fluid among the participants. There were 15% grade I placental calcification, 28.7% were grade II and 56.3% grade III among the participants (Table 5).

Table 6: Thalamic echogenicity, Fetal presentation, and fetal viability among the participants.

Variable	N (%)
Thalamic echogenicity	
Echogenic	70 (87.5)
Echolucent	10 (12.5)
Fetal presentation	
Cephalic	48 (60)
Breech	27 (33.8)
Others	5 (6.2)
Fetal viability	76 (95)

There were 87.5% had echogenic and 12.5% had Echolucent among the participants. There were 60% had cephalic presentation, 33.8% had breech presentation and 6.2% had other presentations. There were 95% viable fetuses among the participants (Table 6).

Table 7: Transabdominal ultrasonography fetal parameters at 37 weeks among the participants

Variable	Mean ± SD
Gestational age (By LMP)	36.6±0.5
Biparietal diameter (mm)	92.3±4.9
Femur length (mm)	66.1±6.9
Abd. Circumference (mm)	297.3±48.2
Head circumference (mm)	290±7.3

The mean gestational age was 36.6±0.5 weeks among the participants. The mean BPD was 92.3±4.9 among the participants. The mean femur length was 66.1±6.9 among the participants. The mean abdominal circumference was 297.3±48.2 among the participants. The mean head circumference was 290±7.3 among the participants (Table 7).

Table 8: Transabdominal ultrasound at 37 weeks between the participants

Variable	n= 80
Amniotic fluid vernix	
Yes, n (%)	76 (95)
No, n (%)	4 (5)
AFI, Mean ± SD	135.7±24.8
Turbidity, n (%)	13 (16.3)
Placental calcification	
Grade I, n (%)	7 (8.7)
Grade II, n (%)	27 (33.8)
Grade III, n (%)	46 (57.5)
Thalamic echogenicity	
Echogenic, n (%)	75 (93.8)
Echolucent, n (%)	5 (6.2)

There were 95% had amniotic fluid vernix and 5% had no amniotic fluid vernix among the participants. The mean AFI was 135.7±24.8 among the participants. There were 16.3% had turbid amniotic fluid among the participants. There were 8.7% grade I placental calcification, 33.8% were grade II and 57.5% grade III among the participants. There were 93.8% had echogenic and 6.2% had Echolucent among the participants (Table 8).

Table 9: Preterm delivery, RDS, NICU admission and neonatal mortality among the participants

Variable	N= 80 n (%)
NICU admission	27 (33.8)
NICU duration	
<24 hours	7 (8.7)
24- 48 hours	13 (16.3)
>48 hours	7 (8.8)
RDS	15 (18.8)
Neonatal mortality	1 (1.3)

There were 33.8% admitted to NICU among them 8.7% for less than 24 hours, 16.3% admitted for 24 to 48 hours, and 8.8% for more than 48 hours. There were 18.8% had RDS. The neonatal mortality was among 1.3% of the participants (Table 9,).

Table 10: Fetal outcome among the participants

Variable		N=80
1-min APGAR	Mean ± SD	6.0±1.5
	<7, n (%)	62 (77.5)
5-min APGAR	Mean ± SD	6.3±1.6
	<7, n (%)	59 (73.8)
Fetal weight (gm)	Mean ± SD	3164.5±605.1
Fetal gender	Male, n (%)	44 (55)
	Female, n (%)	36 (45)

The mean 1-min APGAR score was 6.0±1.5 and there were 77.5% had 1-min APGAR less than 7. The mean 5-min APGAR score was 6.3±1.6 and there were 73.8% had 5-min APGAR less than 7. The mean fetal weight was 3164.5±605.1 grams. There were 55% males and 45% females among the participants (Table 10).

Table 12: The sensitivity and specificity of the thalamic echogenicity via ultrasonography as a marker for lung maturity

Variable	AUC	Sensitivity (%)	Specificity (%)	Sig.
Echogenic thalamus	79.2	60	98.5	<0.001*

The ultrasonic criteria measured during the study, the specificity and the sensitivity values are higher for the thalamic density. The AUC was 79.2%, Sensitivity was 60% while the specificity was 98.5% (Table 12, Figure 1).

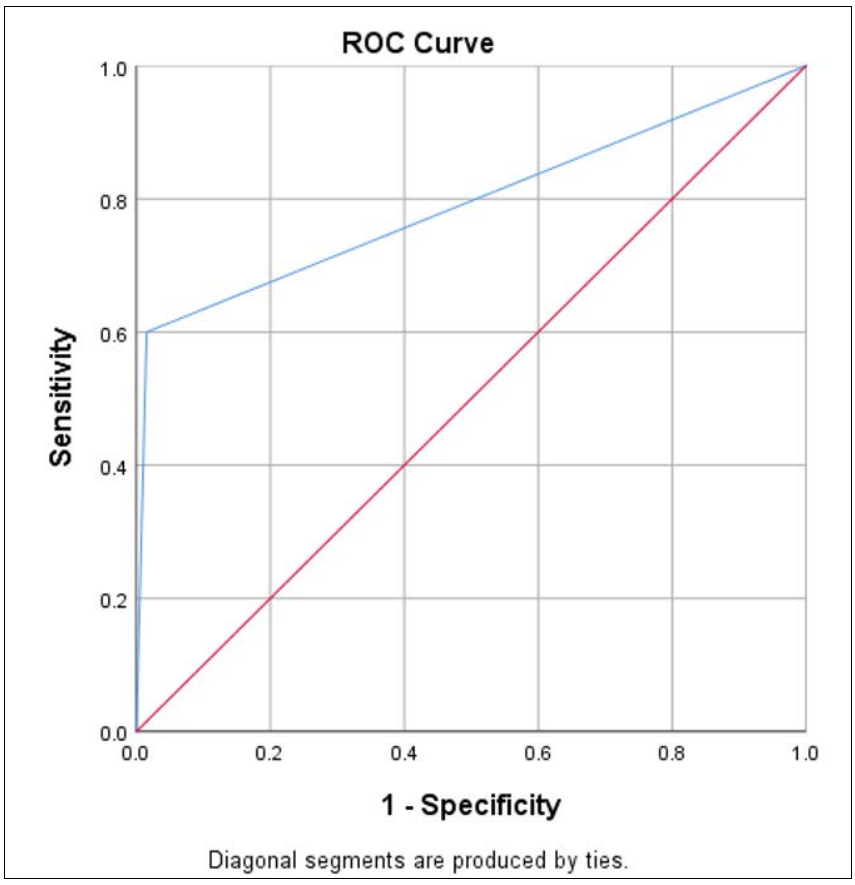

Fig 1: ROC curve analysis of thalamus echogenicity as a marker for predicting lung maturity

Discussion

Noninvasive direct assessment of fetal lung maturity was studied by the ultrasonic fetal lung frequency component, B-mode image texture and special mean gray level, where the ultrasonic methods should rely on a special computer system or the mean gray level was so unstable to the device gain and the depth of the subjects that every measurement needed test piece calibration. Ultrasonography has contributed by the use of chest circumference and area or by comparison with other fetal measurements [9].

However, little is known about the growth pattern of thalami during fetal life, and virtually nothing is known about the possible association of deviations from the normal growth pattern with the abnormal conditions mentioned above. The only published study on fetal thalami compared the volumes of cerebral structures, including thalami, in 39 normally growing and 39 growth-restricted fetuses and reported lack of significant difference in thalamic volumes between the two groups, together with rather moderate reproducibility of the measurements [10].

It would be convenient to predict fetal lung immaturity before an elective birth noninvasively to allow therapeutic protection against possible respiratory distress syndrome (RDS) in the neonate, or in some cases, to estimate the effect of adrenal steroid treatment of a preterm fetus by repeated tests that can be freely performed by noninvasive techniques. Prenatal diagnosis permits delivery by planned caesarean section sufficiently early to avoid the possible complications (120). A review of [11] reported that 155 cases found that prenatal diagnosis results in a 95% reduction in late fetal and neonatal mortality. Such observations have inspired several clinical groups and parents to recommend routine identification of umbilical cord insertion at 20 weeks of gestation and targeted screening for vasa previa in women identified as at high risk for the condition. Many studies of ultrasound prediction of fetal lung maturity were used to compare ultra-sound parameters with tests of amniocentesis to assess that sign with lung maturity [12].

As there are still no studies, either ultrasound or MRI, on the reference curves for the volume of thalami in normal fetuses, we carried out this study to evaluate the validity of measuring fetal thalamic echogenicity by ultrasound as a marker of fetal lung maturity.

This was a prospective observational study that was being carried out on 80 pregnant patients. They were recruited from Obstetrics and Gynaecology clinics at Tanta University Hospitals during the period of research from March 2021 till the end of the study.

Analysis of our findings, we found that the mean age was 32.7±5.6 years among the participants. The age ranges from 22 to 40 years with median 34 years. The mean BMI was 23.1±1.9 among the participants. The BMI was ranging from 20 to 26 with median 23. There were 25% primigravida among the participants. There were 20% nullipara among the participants. There were 32.5% had previous history of abortion among the participants. There were 33.8% had previous history of caesarean among the participants.

In agreement with our findings, the study of [13] which aimed to study the Doppler indices of the main fetal pulmonary artery and their role in predicting respiratory distress syndrome in severe pre-eclampsia, and reported that the mean age is 28.57 years with median gravidity & parity 3 and 2, respectively. The mean gestational age was 36.09-week.

Another study done by -, aimed to assess the efficacy of the amniotic fluid lamellar body counting (LBC) from vaginal pool in predicting fetal lung maturity in women with preterm premature rupture of membranes, and reported that the age ranges from 18 to 37 years with mean 27.0±4.1 years, the mean BMI was 26.2±2.1 among the participants. The BMI was ranging from 21.8–31.3. There were 34.8% primigravida among the participants.

Furthermore, the study of (15) the mean maternal age was 27.89 years±4.37 (range 20–37) years. Mean gestational age was 35.45 weeks±1.72 (range 30–37). Most women had one or more parity, but nulli-parous women represented about one-fourth (25.8%) of the study subjects. Twenty-three patients reported a history of abortion.

In the current study, the mean gestational age was 34.6±0.4 weeks among the participants. The mean BPD was 77.6±12.8 among the participants. The mean femur length was 62.5±6.8 among the participants. The mean abdominal circumference was 294.6±20.6 among the participants. The mean head circumference was 270±2.1 among the participants.

While (16) reported that the mean gestational age was 30.29±3.34 weeks, the mean BPD was 29.98±3.39 among the participants. The mean femur length was 30.52±3.43 among the participants. The mean abdominal circumference was 29.58±3.25 among the participants. The mean head circumference was 30.73±3.46 among the participants.

During the third trimester of pregnancy, ultrasound is commonly performed in patients that present both asymptomatically or with symptoms. There are currently no major guidelines or protocols to standardize the use of ultrasound at this stage of pregnancy. Ultrasound can be useful to identify fetal and maternal pathology and to follow the progression of the pregnancy [17].

In the current study, there were 88.8% had amniotic fluid vernix and 11.2% had no amniotic fluid vernix among the participants. The mean AFI was 130.7±7.3 among the participants. There were 13.8% had turbid amniotic fluid among the participants. There were 15% grade I placental calcification, 28.7% were grade II and 56.3% grade III among the participants [18], has been reported that both grade II and III placenta predicted fetal lung maturity in 100% of cases, suggesting that placental grading could replace estimation of the L/S ratio and thereby avoid amniocentesis and its complications. However, subsequent workers in this field have cast doubt on the reliability of placental grading as a predictor of fetal lung maturity, and the subject has become controversial for a many reasons including presence of complications like hypertension, diabetes mellitus or Rh iso-immune disease. Accordingly, the search for novel signs and markers for prediction of lung maturity became an interested discipline in the obstetrics field.

Accordingly [19], reported that the search for novel signs and markers for prediction of lung maturity became an interested discipline in the obstetrics field. The present study confirmed the previously reported data that grades II and III placentas were highly associated with fetal lung maturity. Meanwhile, the finding of fetal lung maturation in 83.3% of infants in grade III group justifies using this group to indicate fetal lung maturity before repeat caesarean section in woman with reasonable certainty to reach 38 weeks of gestation and has no complicating diseases.

Reported [20] that scanning with linear ultrasound with convex transducer frequency of 3.5 MHz was utilized to measure the bi-parietal diameter and the state of echogenicity was recorded as echogenic or echolucent, in addition to amniotic fluid vernix and the placental changes.

Utilized [21] amniocentesis for determination of fetal lung maturity and ultrasonographic (US) evaluation of the biparietal diameter (BPD) and placental grade were performed

simultaneously and concluded that the ability of the sonographic parameters to predict fetal lung maturity was closely related to menstrual age and the best use of US for predicting fetal lung maturity is in establishing menstrual age early in pregnancy; the results obtained in the present study support the previously mentioned idea. Concerning evaluation of the presence of FFPs in the amniotic fluid [22], correlate this ultrasound finding with fetal lung maturity and suggest that presence of FFPs on real-time ultrasound could be used to confirm fetal lung maturity.

Reported (23 that fetuses with mature lungs (the non-RDS group), the following diagnostic thresholds predicted lung maturity with (p value = 0.001) respectively BPD 82.8 to 93.5 mm, AC 294 to 322 mm, and FL 62.7 to 73.1 mm. The diagnostic threshold predicts RDS, BPD 77.3–86.3 mm, AC 257–299 mm, and FL 54–65.8 mm.

Neonatal respiratory distress syndrome (RDS) remains a major cause of mortality and morbidity in the newly born infants due to immaturity of their lungs. It occurs mainly in newborns who are delivered pre-maturely, and it is associated reversely with gestational age at birth. The decision to continue or delay delivery depends usually the ability to properly evaluate fetal lung maturity. Lung maturity was commonly assessed roughly by gestational age, and the substitute was amniocentesis but it is invasive, can be performed only by trained persons, is costly, and may have complications [24].

Compared to the findings of the present study, much less figures were identified by other researchers, where [25] found an RDS incidence of 7% and (138) reported even lesser incidence (3.7%) among neonates at 36 weeks of gestation.

In addition to above findings, the study on our hands revealed that the mean 1-min APGAR score was 6.0±1.5 and there were 77.5% had 1-min APGAR less than 7. The mean 5-min APGAR score was 6.3±1.6 and there were 73.8% had 5-min APGAR less than 7. The mean fetal weight was 3164.5±605.1 grams. There were 55% males and 45% females among the participants

Regarding fetal thalamic echogenicity, the (26) study reported sensitivity, specificity, and accuracy of 77%, 79%, and 80%, respectively, for lung maturity prediction. They observed that thalamic density increased with increased fetus age in our daily practice, so the current study tried to evaluate this sign along with other ultrasound and Doppler parameters as indicators for fetal lung maturity.

Reported [27] comparable results regarding thalamic echogenicity as an ultrasound marker of fetal lung maturity. Their findings showed sensitivity, specificity, and accuracy of 77.3%, 75%, and 77%, respectively.

Moreover, it was consistent with [28] who identified fetal lung maturity using thalamic echogenicity with a reported sensitivity, specificity and PPV of 63.33%, 86.53%, and 89.6%, respectively.

The strengths of current study are the following: (1) nearly the first paper in our university—to the best of our knowledge—which discusses multiple parameters in a try to assess fetal lung maturity. (2) This study has a prospective design and minimal maternal/fetal co-morbidities in the study subjects, which could increase the applicability and validity of this technique prior to elective delivery of preterm fetuses especially in the event of NICU unavailability. (3) A single sonographer conducted all the ultrasound measurements, thus reducing the inter-observer and intra-observer variation.

Conclusions

Evaluation of echogenic thalamus by ultrasound at the level of the BPD is of value, and can be considered as a new marker of fetal lung maturity; however, further studies are required to strengthen such idea.

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Conflict of Interest: Nil

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