

# Can Thalamic Echogenicity by Ultrasound Be Used as a Predictor of Fetal Lung Maturity?

Original  
Article

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## ABSTRACT

**Aim:** The present study aimed to evaluate using thalamic echogenicity by ultrasound as a predictor of fetal lung maturity in comparison with other ultrasound markers.

**Methods:** This was a prospective study performed in Ain Shams Maternity Hospital, Cairo, Egypt from August, 2020 until April 2021. Two hundred and thirty-eight pregnant women (36 to 40 weeks of gestation) who were admitted for elective cesarean section were recruited. An obstetric ultrasound scan was done at the same day of their elective cesarean section to evaluate echogenicity of the thalamus, to measure presence of ossification centers of distal femur epiphysis (DFE) and proximal tibia epiphysis (PTE), to measure biparietal diameter, to detect placental changes and amniotic fluid vernix. The outcome measures were APGAR scores at 1 minute and 5 minutes, admission to neonatal intensive care unit, duration of hospitalization and signs of respiratory distress syndrome (RDS).

**Results:** The presence of echogenic thalamus as a sign of fetal lung maturity had a specificity of 77.2% which was lower than specificity of presence of PTE (90.4%) and measurement of BPD (82.6%). Diagnostic accuracy was 77.3% which was also lower than PTE (90.8%) and BPD (81.5%), respectively. Sensitivity was 78.9% which was lower than PTE (99.5%) and BPD (82.6%), respectively. Negative predictive value for thalamic echogenicity, PTE and DFE were 97.7%, 99.5% and 99.2%, respectively.

**Conclusion:** Evaluation of echogenic thalamus could be an accurate method to predict fetal lung maturity. However, further studies are required to strengthen such idea.

**Key Words:** Accuracy; biparietal diameter; fetal lung maturity; thalamic echogenicity; ultrasound.

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## INTRODUCTION

Premature delivery is one of the major health problems that is associated with huge health complications and a major financial burden; the WHO estimates its financial burden to be around 40-50 billion \$ per year worldwide<sup>[1]</sup>. Respiratory distress syndrome (RDS), formerly known as hyaline membrane disease, is the most common cause of respiratory distress in preterm infants because lung immaturity is associated with inadequate production of pulmonary surfactant. RDS may be prevented, or its severity decreased with the use of antenatal steroid therapy, early administration of positive airway pressure and, in some cases, exogenous surfactant therapy<sup>[2]</sup>.

It would be convenient to predict fetal lung immaturity before an elective birth noninvasively, to allow therapeutic protection against possible RDS in the neonate, or in some cases, to estimate the effect of steroid treatment of a preterm fetus by repeated tests that can be freely performed by noninvasive techniques. Prenatal diagnosis

permits delivery by planned cesarean section sufficiently early to avoid the possible complications<sup>[3]</sup>. The gold-standard methods to assess fetal lung maturity are still the chemical, biological and physical properties of amniotic fluid obtained by amniocentesis<sup>[4]</sup>.

There are several other indirect methods that can predict fetal maturity. In the second and third trimesters, estimation of gestational age is accomplished by measuring the biparietal diameter (BPD). BPD of at least 9.2 cm will undoubtedly predict the lack of RDS in uncomplicated gestations<sup>[3]</sup>. In addition, the thalamus is a central brain region that plays a crucial role in distributing incoming sensory information to appropriate regions of the cortex<sup>[5]</sup>. Some studies reported that the fetal thalamus showed significant changes of echogenicity late in pregnancy which may have a place in assessing fetal maturity<sup>[3]</sup>. Many studies suggested the use of placental maturity grading systems to evaluate the fetal lung maturity<sup>[6]</sup>. Many grading systems has been proposed, the most accepted one is the Grannum Classification system, which classifies placental

maturity into four grades 0 - III, based on the ultrasound appearances of the placenta<sup>[6]</sup>.

Fetal skeletal bones become visible with ultrasound only when they are calcified. While the primary ossification center develops early in pregnancy, the secondary ossification center forms in late pregnancy and early neonatal life. The secondary ossification centers are hypoechogenic structures during intrauterine life. Only the secondary ossification centers within the epiphyseal cartilage of the proximal tibia and distal femur could be assessed by ultrasound<sup>[7]</sup>.

Vernix caseosa is an oil-rich aggregate substance that is observed on the fetal surface throughout the 3rd trimester of gestation. While the pregnancy advances, the quantity of squalene in the vernix raises opposed to cholesterol which in turn minimizes the adhesion of the vernix to the fetal surface. Next, the vernix will pass from the fetal surface into the amniotic fluid. Many studies have been concluded that the amniotic fluid turbidity correlates well with the lung maturity as well as the complete maturity of the fetus<sup>[8]</sup>.

In an attempt to establish further non-invasive method for evaluation of fetal lung maturity, the present study was designed to evaluate the validity of measuring fetal thalamic echogenicity by ultrasound as a predictor of fetal lung maturity.

## MATERIALS AND METHODS

This was a prospective study performed in Ain Shams Maternity Hospital in Cairo, Egypt from August, 2020 until April, 2021. Ain Shams Ethical Committee approval was obtained. Informed written consents were obtained from all participants. Two hundred and thirty-eight pregnant women at 36 to 40 weeks of gestation were recruited. Women with uncomplicated singleton pregnancies who were to deliver by cesarean section under spinal anesthesia, to omit the effect of general anesthesia on the neonate, were included. First trimester ultrasound records of crown rump length were mandatory to calculate gestational age for all women. All women with multiple gestations, fetal malformations, medical disorders, intrauterine growth restriction or macrosomic fetuses, antepartum hemorrhage or presence of meconium-stained liquor were excluded. Ultrasound was done for fetal maturity signs on the same day of delivery and the neonate was examined after delivery. Ultrasound examination was done with convex transducer Pro 6 variable frequency, CA 1~7 MHZ (Samsung H6O) at Fetal Medicine Unit of Ain Shams Maternity Hospital. The ultrasound examination was conducted by the same ultra-sonographer to decrease the interobserver variation. Ultrasound examination included the following criteria for fetal lung maturity:

- Thalamic density at the level of the trans-thalamic plane, on each side of the third ventricle. Density was evaluated as echogenic if similar to the rest of the brain tissue in echogenicity, or echo-lucent if it was less echogenic to the rest of the brain tissue.

- Ossification centers in distal femoral epiphysis (DFE) was identified by visualizing the distal femur epiphysis as an egg-shaped echo rich area centrally placed within the hypoechogenic epiphyseal cartilage of the femur at its distal extremity. Its exact identification was made by guiding the transducer along the largest axis of the femoral diaphysis avoiding oblique sectioning.
- Proximal tibial epiphysis (PTE) that was also an echogenic structure adjacent to the tibial head and measured similarly. Measurements of EOC were obtained in an axial plane from outer to outer margins along the medial-lateral surfaces of the epiphysis. Care was always taken not to mistake the ossification centers for the echogenic material within the intercondylar notch, or even for the patella or transversal sectioning of the long bones near the epiphyses.
- Placental changes according to the Grannum classification,
- BPD which was measured in millimeters
- Vernix in the amniotic fluid.

The pediatrician examined each neonate for the following fetal outcomes: Apgar scores at one and five minutes, signs of a respiratory distress, admission to the neonatal intensive care unit (NICU), duration of hospitalization, and any adverse neonatal morbidity or mortality up to discharge. The six ultrasound parameters for assessing fetal maturity (BPD, placental changes, amniotic fluid vernix, thalamus echogenicity, ossification center of distal femoral and proximal tibial epiphyses) were correlated to the neonatal outcome.

### Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Quantitative normally distributed data described as mean±SD (standard deviation) after testing for normality using Shapiro-Wilk test, then compared using independent t-test if normally distributed. Qualitative data described as number and percentage and compared using Chi square test and Fisher's Exact test for variables with small expected numbers. The level of significance was taken at *P value* < 0.050 was significant, otherwise was non-significant.

Diagnostic characteristics was calculated as follows:

1. Sensitivity = (True positive test / Total positive golden) x 100
2. Specificity = (True negative test / Total negative golden) x 100
3. Diagnostic accuracy = ([True positive test + True negative test] / Total cases) x 100
4. Youden's index = sensitivity + specificity - 1

5. Predictive positive value = (True positive test / Total positive test) x 100
6. Predictive negative value = (True negative test / Total negative test) x 100
7. LR+ = (sensitivity/ 1-specificity)
8. LR- = (1- sensitivity / specificity)
9. LR= LR+ / LR-
10. Kappa=Observed agreement-chance agreement / 1-chance agreement

**RESULTS**

Twenty-two participants were lost to follow up as follows; five participants received general anesthesia; one participant had congenital fetal malformations; five patients had oligohydramnios; eight patients had meconium stained liquor at delivery; three fetuses were macrosomic. All were excluded from analysis.

The mean maternal age was 29.4±4.1years and mean gestational age was 38.1±1.3 weeks. 13.9% were nulliparous and 86.1% of women were multiparous (Table 1). Apgar score at 1 minute was < 7 in 88 neonates and ≥ 7 in the remaining 150 neonates. 68 neonates had an Apgar score at 5 min <7, while 170 neonates had a score of ≥7. On the other hand, 15% of all neonates were admitted to the NICU. 11.6% were admitted for < 24 hours, 3.4% were admitted for more than 24 (Table 2). In 19 neonates (8 %), the clinical examination indicated RDS, while the remaining 219 (92%) neonates had no RDS.

Regarding ultrasound parameters results and correlation with RDS according to gestational age among the studied cases, at 36 weeks 3 cases had RDS out of 17 cases who had echogenic thalami while 9 cases had RDS from 20 cases who had echolucent thalami. At 37 weeks, one neonate had RDS out of 30 patient who had echogenic

thalami , while 6 neonates had RDS out of 16 patients who had echolucent thalami. There were no cases of RDS from 136 cases who had echogenic thalami and 29 cases who had echolucent thalami at gestational age from 38 until 40 weeks of gestation (Table 3).

**Table 1:** Demographic characteristics of the studied cases

Characteristics	Mean±SD	Range	
Age (years)	29.4±4.1	20.0–41.0	
BMI (kg/m <sup>2</sup> )	28.4±3.3	19.2–36.6	
GA (weeks)	38.1±1.3	36.0–40.0	
	N	%	
Parity	Nulli	33	13.9
	One	60	25.2
	two	73	30.7
	Three	47	19.7
	≥4	25	10.5
Gravidity	1-2	77	32.3
	3-4	108	45.4
	≥5	53	22.3
History of previous abortions	85	35.7	

**Table 2:** Neonatal outcomes among the studied cases

Outcomes	N	%
APGAR-1 < 7	88	37.0
APGAR-5 < 7	68	28.6
RDS	19	8.0
NICU admission	36	15
NICU admission ≥24 hours	8	3.4

Total=238. RDS: Respiratory distress syndrome. NICU: Neonatal intensive care unit

**Table 3:** Correlation between US parameters results and RDS according to gestational age

Ultrasound parameters	36 weeks (n=37)		37 weeks (n=46)		38 weeks (n=47)		39 weeks (n=69)		40 weeks (n=39)		
	No RDS	RDS									
Thalamic echogenicity	Echogenic	14	3	29	1	34	0	59	0	33	0
	Echolucent	11	9	10	6	13	0	10	0	6	0
Proximal tibia Epiphysis	>5 mm	17	1	32	0	44	0	66	0	39	0
	<5mm	8	11	7	7	3	0	3	0	0	0
Distal femur epiphysis	>6.25 mm	9	1	20	0	31	0	49	0	21	0
	<6.25	16	11	19	7	16	0	20	0	18	0
Biparietal diameter	>9.2 cm	18	2	26	4	40	0	61	0	36	0
	<9.2cm	7	10	13	3	7	0	8	0	3	0
Amniotic fluid Vernix	Present	11	2	20	3	28	0	51	0	32	0
	Absent	14	10	19	4	19	0	18	0	7	0
Placental grading	Grade II&III	10	3	19	2	36	0	65	0	37	0
	Grade 0&I	15	9	20	5	11	0	4	0	2	0

Table 4 shows comparisons between different ultrasound parameters indicating fetal maturity regarding accuracy. Thalamic echogenicity had sensitivity of 78.9%, specificity of 77.2% and accuracy of 77.3% with NPV of

97.7%. Fetal tibial epiphysis was highly sensitive (94.7%), highly specific (90.4%) and had the highest accuracy (90.8%) with PPV (46.2%) and good NPV (99.5%). Fetal femoral epiphysis was also highly sensitive (94.7%).

**Table 4:** Diagnostic characteristics of maturity predictors in predicting RDS

Characteristics	Thalamic echogenicity (echogenic)	Fetal tibia epiphysis $\geq 5$ mm	Fetal femur epiphysis $\geq 6.25$ mm	Biparietal diameter $\geq 92$ mm	Amniotic fluid vernix (present)	Placenta grading II – III
Sensitivity	78.9%	94.7%	94.7%	68.4%	73.7%	73.7%
Specificity	77.2%	90.4%	59.4%	82.6%	64.8%	76.3%
DA	77.3%	90.8%	62.2%	81.5%	65.5%	76.1%
YI	56.1%	85.1%	54.1%	51.1%	38.5%	49.9%
PPV	23.1%	46.2%	16.8%	25.5%	15.4%	21.2%
NPV	97.7%	99.5%	99.2%	96.8%	96.6%	97.1%
LR+	3.46	9.88	2.33	3.94	2.10	3.10
LR-	0.27	0.06	0.09	0.38	0.41	0.35
LR	12.68	169.71	26.29	10.32	5.16	8.99
Kappa	0.267	0.575	0.174	0.289	0.141	0.235

DA: Diagnostic accuracy. YI: Youden's index. PPV: Positive Predictive value. NPV: Negative Predictive value. LR+: Positive likelihood ratio. LR-: Negative likelihood ratio. LR: Diagnostic odd ratio

## DISCUSSION

The present study was designed to evaluate the accuracy of measuring some fetal parameters by ultrasound as markers of fetal lung maturity. These parameters include fetal thalamic echogenicity, epiphyseal ossification centers of femur and tibia, placenta grading, BPD and amniotic fluid vernix. The present study reported that the delivered neonates, 37% had an Apgar score at 1 minute of  $< 7$ , while only 28.6% had a score  $< 7$  at 5 minutes. From another point of view, RDS was used as an indicator in this study for fetal lung immaturity and showed only 8% had RDS which decreased with advanced gestational age. This result agrees with the study of Abdulla *et al.*<sup>[9]</sup>, who gave comparable outcomes and found an incidence of 6% for infants born at 34 – 36 weeks gestation and 6 % at 36-40 weeks. Other studies showed a lower incidence of RDS such as Edwards *et al.*<sup>[10]</sup>, which documented that RDS occurs in up to 7% of newborn infants and Ghafoor *et al.*<sup>[11]</sup>, which reported an incidence rate of RDS 3.7% among neonates at 36 weeks of gestation.

In the present study, RDS was cross-tabulated against the sonographic finding of each parameter. The gestational age rather than the maternal age was found to be a major risk factor for both development of RDS and NICU admission with P value of 0.001 and 0.863 respectively.

Regarding the prediction of RDS, thalamic echogenicity was found to have moderate sensitivity (78.9%), moderate specificity (77.2%), positive predictive value of 23.1%, negative predictive value of 97.7% and diagnostic accuracy of 77.3%.

The epiphyseal ossification centers (PTE and DFE) were found to have the highest sensitivity (94.7%), high specificity (90.4%) for PTE and lowest specificity (59.4%)

for DFE, positive predictive value of 46.2% for PTE, low positive predictive value of 16.8% for DFE and the highest negative predictive value of 99.5% for PTE, high negative predictive value of 99.2%, diagnostic accuracy of 90.8% for PTE and 62.2% for DFE.

BPD  $> 9.2$  cm correlating with fetal lung maturity was found to have sensitivity of 68.4%, specificity of 82.6%, positive predictive value of 25.5%, negative predictive value of 96.8% and diagnostic accuracy of 81.5%.

The amniotic fluid particles (vernix) were found to have good sensitivity (73.7%), the lowest specificity (64.8%), the lowest positive predictive value of 15.4%, negative predictive of 96.6% and diagnostic accuracy of 65.5%. The placental maturity grade II and III were found to have good sensitivity (73.7%), good specificity (76.3%), positive predictive value of 21.2%, negative predictive of 97.1% and diagnostic accuracy of 76.1%.

This result agrees with the study of Abdulla *et al.*<sup>[9]</sup>, in which the fetal tibia epiphysis was the best predictor compared to other five parameters (with 95.5%, 91.7% and 95% for sensitivity, specificity, and accuracy respectively), followed by fetal femur epiphysis (with sensitivity of 97.7%, specificity 50% and accuracy of 92%). Mahony *et al.*<sup>[12]</sup> assessed sonographic epiphyseal ossification centers in the assessment of fetal lung maturity in correlation with the amniocentesis lung profile. They found that proximal tibia epiphysis had an accuracy of positive predicting a mature amniocentesis lung profile of 100% and specificity of 100% while sensitivity and accuracy of prediction of an immature amniocentesis lung profile were low (22-25%) for the same epiphyseal parameters.

Furthermore, some investigators used EOC as markers of fetal gestational age and indirectly predict fetal maturity.

A study done by Ahmad T *et al.*<sup>[13]</sup> found that sonographic evaluation of distal femoral and proximal tibial epiphyseal centers can be practiced as sufficient markers for the calculation of gestational age during the third trimester. Another study by Tabsh KM *et al.*<sup>[14]</sup> found that ossification centers around the fetal knee (DFE and PTE) as measured by ultrasound correlated well with amniotic fluid lecithin: sphingomyelin ratio. Several precautions should be taken; while the presence of these centers may be helpful in determining fetal lung maturity, their absence does not indicate that a fetus necessarily does not have mature lung. Additionally, adjacent structures to the cartilaginous centers should not be misinterpreted as the epiphyseal centers.

In Abdulla *et al.*<sup>[9]</sup>, it was shown that sensitivity; specificity and accuracy of fetal thalamic echogenicity in the prediction of fetal lung maturity were 77.3%, 75.0%, and 77.0% respectively; which were the same as the present study.

At 2001, Faris Anwer<sup>[15]</sup> did a prospective study to evaluate fetal thalamus ultrasonic change with increasing age and concluded by that study that fetal thalamus showed statistically significant differences of echogenicity late in pregnancy which may have a place in assessing fetal maturity. Another study done by Rasheed *et al.*<sup>[3]</sup> showed that sensitivity and specificity of fetal thalamic echogenicity in the prediction of fetal lung maturity were: 63.33%, 86.53% respectively and those results are similar to our study results.

Patil, *et al.*<sup>[16]</sup> showed that sensitivity and specificity of fetal thalamic echogenicity in the prediction of fetal lung maturity were: 81.2% and 77.7%, respectively and diagnostic accuracy of 80.9% and these results were close to our study results.

The present study showed that BPD  $\geq$  9.2 cm correlates with fetal lung maturity. In another research done by Slocum *et al.*<sup>[17]</sup> a threshold BPD of greater than or equal to 9.2 cm in all parturient who underwent elective repeat cesarean delivery was associated with no hyaline membrane disease (HMD). Additionally, Prakash *et al.*<sup>[7]</sup> mentioned that sonographically determined parameters: fetal biparietal diameter and placental grading, have been related to fetal maturity, with accuracy ranging from 78% to 100%.

Regarding amniotic fluid vernix, the present study revealed the sensitivity of 73.7% and specificity of 64.8% for prediction of fetal lung maturity. Abdulla *et al.*<sup>[9]</sup> also found that amniotic fluid vernix had a role in the prediction of fetal lung maturity with a sensitivity of 63.6% and specificity of 66.3%.

Ram *et al.*<sup>[18]</sup> assessed the amniotic fluid particles and its predictive value for fetal lung maturity and found a sensitivity of 85.74% which was higher than this study findings and PPV of 66.67% higher than this study which was 15.4% in the prediction of RDS. This variation

might be attributed to the difference in the used technique (amniocentesis versus ultrasound) or inter-observer variations.

A study of Shweni *et al.*<sup>[19]</sup> documented that all the fetuses with placental grade II and III had achieved lung maturity which suggested that placental grading could replace estimation of lecithin /sphingomyelin (L/S) ratio and reduce the number of amniocenteses needed. However, Clair *et al.*, and Kazzi<sup>[20]</sup> disagreed with these results, and cast doubt on the reliability of placental grading as a predictor of fetal lung maturity for a many reasons, including presence of complications like hypertension, diabetes mellitus or Rh iso-immune disease which will affect the fetal lung maturity in the presence of placental maturity grade III. Also, Loret de Mola *et al.*<sup>[21]</sup> found that placental grade III had sensitivity 64% and specificity 98%, but in the present study placental maturity had sensitivity 73.7% and specificity 76.3% in the prediction of fetal lung maturity.

## CONCLUSION

Our study shows that ultrasound assessment for fetal lung maturity is a useful noninvasive procedure with good accuracy. All the six evaluated ultrasonic parameters could be considered as predictors for fetal lung maturity with different extent in their performance. The ultrasonic identification of the ossification centers of the proximal tibia showed the best performance in predicting the fetal lung maturity, followed by distal femur epiphysis and thalamic echogenicity and then the other three parameters: biparietal diameter, amniotic fluid vernix, and placental grading.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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