Evaluation of Quantitative Lung Index as a Gestational Age–Independent Sonographic Parameter to Characterize Fetal Lung Growth

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Abstract: The most common cause of mortality and neonatal morbidity in preterm and early term fetuses is lung immaturity. The current methods used to test fetal lung maturity (FLM), including lamellar body count, lecithin-sphingomyelin ratio, or TDx fetal lung maturity assay II test are performed in amniotic fluid and, consequently, require an invasive procedure. The prediction of lung maturity by noninvasive ultrasound methods has been extensively explored. Earlier studies comparing fetal lung echogenicity with the placenta, fetal gut, or liver demonstrated ultrasonographic changes associated with fetal lung maturation. Other studies used free floating particles in amniotic fluid as a method to evaluate fetal lung maturity by ultrasound. Also the distal femoral epiphyseal secondary ossification center (DFE), may assist in predicting third-trimester gestational age. A new index, the quantitative lung index (QLI) was derived using HC and the area of the base of the right lung. QLI is relatively stable over a wide gestational age window. QLI can be calculated using the following formula: QLI = Right lung area/(HC/10)^2. The aim of the current study was clinical evaluation of Quantitative Lung Index as a gestational age–independent sonographic parameter to characterize fetal lung growth. The study was conducted at Obstetrics and Gynecology department, El Galaa Teaching Hospital, during the period between January 2014 and January 2017. Three hundred cases were included in the study. For the purpose of statistical analysis studied sonographic parameters were associated with adverse neonatal outcome (defined as TTN, RDS, BPD or mortality), serious adverse neonatal outcome (defined as RDS, BPD or mortality), and serious adverse respiratory outcome (defined as RDS or BPD). Each of studied parameters, AFFFP, DFE and QLI in included women were significant good predictors of adverse neonatal outcome, serious adverse neonatal outcome and serious adverse respiratory outcome. In order to propose a scoring system for predicting serious adverse respiratory outcome, multiple logistic regression analysis was performed to estimate the weight of association between measured variables and serious adverse respiratory outcome. A scoring system was proposed. ROC curve was performed to estimate the validity of the proposed scoring system in prediction of serious adverse respiratory outcome and showed significant predictability.

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Key words: fetal lung maturity, quantitative lung index, right lung area, free floating particles, distal femur epiphysis, lung to live echogenicity, scoring system

1. Introduction

The most common cause of mortality and neonatal morbidity in preterm and early term fetuses is lung immaturity. The strongest predictor of lung maturity is gestational age. Thus, infants who are born at less than 39 weeks have significantly higher rates of neonatal morbidity, including respiratory distress syndrome (RDS) when compared with infants born at a gestation of 39 weeks or longer **(Palacio et al., 2012)**.

The current methods used to test fetal lung maturity (FLM), including lamellar body count, lecithin-sphingomyelin ratio, or TDx fetal lung maturity assay II test are performed in amniotic fluid and, consequently, require an invasive procedure **(Wijnberger et al., 2010)**.

Over the last 30 years, the prediction of lung maturity by noninvasive ultrasound methods has been extensively explored. Earlier studies comparing fetal lung echogenicity with the placenta, **(Grannum et al., 1979; Harman et al., 1982; Golde et al., 1984)** fetal gut, **(Zilianti and Fernandez, 1983)** or liver **(Fried et al., 1985; Feingold et al., 1987)** demonstrated ultrasonographic changes associated with fetal lung maturation.

Other studies used free floating particles in amniotic fluid as a method to evaluate fetal lung maturity by ultrasound **(Gross et al., 1985)**.

The distal femoral epiphyseal secondary ossification center (DFE), which can be reliably identified and measured sonographically, may assist in

predicting third-trimester gestational age **(Mahony et al., 1985)**.

A new index, the quantitative lung index (QLI) was derived using HC and the area of the base of the right lung. QLI is relatively stable over a wide gestational age window. It was developed as a gestational age–independent sonographic parameter to characterize lung growth. QLI can be calculated using the following formula: QLI = Right lung area/(HC/10)^2. Further studies are needed to assess the clinical accuracy of the QLI in characterizing fetal lung growth **(Quintero et al., 2011)**.

Aim of the work

Clinical evaluation of Quantitative Lung Index as a gestational age–independent sonographic parameter to characterize fetal lung growth.

2. Subjects and Methods

The study was conducted at Obstetrics and Gynecology department, El Galaa Teaching Hospital, & included Women receiving prenatal care and delivering during the period between January 2014 and January 2017. Three hundred cases were included in the study.

Singleton pregnancies at 28 – 42 weeks, delivering within 72 hours from scan were included in the study.

Cases with major congenital anomalies, hydrops fetalis, premature rupture of membranes, umbilical cord prolapse, placental abruption, oligohydramnios, medical maternal high risk factor (e.g. diabetes mellitus, hypertensive disorders), history of receiving steroid therapy, intra-uterine growth retardation, macrosomic fetuses, or presence of meconium stained amniotic fluid were not recruited in the study.

Gestational age was assigned, only cases with reliable dating were included.

Sonographic examinations were performed with Siemens SONOLINE G50 ultrasound unit by a real-time, 3.5-MHz curvilinear transducer. All ultrasonographic measures are the average of three measurements so meeting limits of agreement for intra-observer and inter-observer variation **(Kiserud and Johnsen, 2009).**

QLI is calculated using the following formula: QLI = Right lung area/(HC/10)^2. Right lung area is measured at the level of the 4-chamber view of the heart. The longest diameter and the longest perpendicular diameter are multiplied **(Quintero et al., 2011).**

During scanning manual tracing of right lung area was performed also as a standard method for sonographic measurement of surface area.

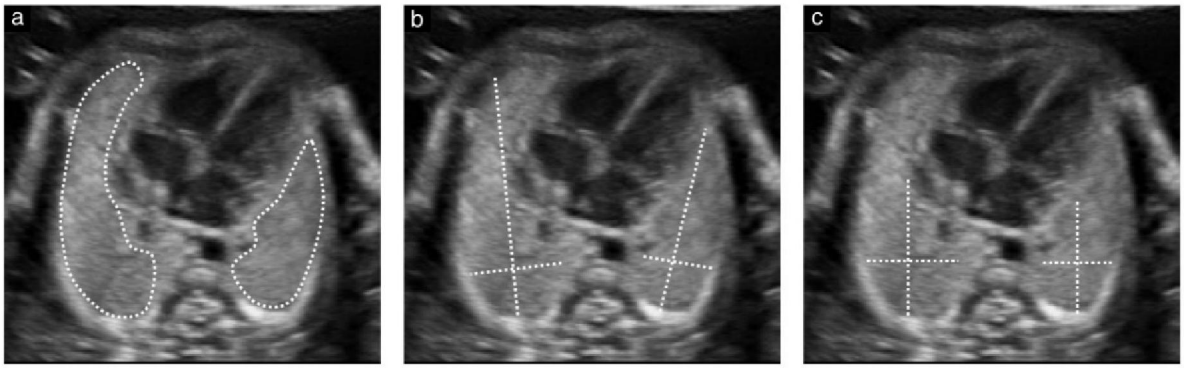

Figure-1 Two-dimensional ultrasound images showing measurement of the lung area in the cross-sectional plane of the thorax (used for examination of the four-chamber view of the heart) (a) by manual tracing of the limits of the lungs, (b) by multiplication of the longest diameter of the lung by its longest perpendicular diameter, and (c) by multiplication of the anteroposterior diameter of the lung at the mid-clavicular line by the perpendicular diameter at the midpoint of the anteroposterior diameter **(Peralta et al., 2005)**.

In this study older sonographic methods used for assessment of lung maturity like, echogenicity of fetal lung compared to fetal liver, appearance of amniotic fluid free floating particles and measuring epiphyseal ossification center of the distal femur (DFE) were re-evaluated.

Several neonatal outcomes were examined, including neonatal death, respiratory distress syndrome (RDS), transient tachypnea of the newborn, bronchopulmonary dysplasia **(Bates et al., 2010).**

3. Results

The mean age of included women was 30.5 ± 5.1 years (range: 19 – 42 years). The median parity was 2 (range: 0 – 5); interquartile range: (1 – 3). The mean gestational age was 35.5 ± 4.28 weeks (range: 28 – 42 weeks). As regarding gestational age distribution of the studied cases, 73 (24.3%) were 28 - < 32 weeks, 41 (13.7%) were 32 - < 34 weeks, 68 (22.7%) were 34 - < 37 weeks, 57 (19%) were 37 – 40 weeks, 61 (20.3%) were > 40 weeks.

The mean sonographically-measured fetal BPD was 87.57 ± 8.26 mm (range: 70.00 – 101.00 mm). The mean fetal HC was 310.39 ± 27.35 (range: 250.40 - 360.00 mm). The mean fetal AC was 314.65 ± 40.23 mm (range: 230.10 - 373.40 mm). The mean fetal FL was 67.73 ± 7.65 mm (range: 51.80 - 79.00 mm). The mean estimated fetal weight (EFW), using Hadlock's formula, was 2128.26 ± 1210.19 g (range: 325.77 - 4345.09 g).

Several sonographic parameters of lung maturity were studied in included women, Lung to liver echogenicity revealed 81 (27%) cases were hypodense, 107 (35.7%) cases were isodense, 62 (20.7%) cases were hyperdense and 50 (16.7%) cases were marked Hyperdense. The mean AFFFP was 1.79 ± 0.81 mm (range: 0.2 – 3.4 mm). AFFP was present in 211 (70.3%) cases and absent in 89 (29.7%). The mean DFE was 5.15 ± 2.83 mm (range: 0.2 – 9.5 mm). DFE was present in 241 (80.3%) cases and absent in 59 (19.7%).

Quantitative lung index (QLI) was derived using HC and the area of the base of the right lung measured at the level of the 4-chamber view of the heart. QLI can be calculated using the following formula: QLI = Right lung area/(HC/10)^2. Is was originally described to measure the area of the base of right lung using multiplication of the perpendicular longest diameters. During scanning manual tracing of right lung area was performed also as a standard method for measurement of surface area. RLA [calculated from Perpendicular Longest Diameters] was 2084.71 ± 579.2 mm2 (range: 1066 – 2955 mm2), while RLA [calculated from Tracing] was 1452.37 ± 345.56 mm2 (range: 790 – 2066 mm2). QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.11 ± 0.26 (range: 1.46 – 2.45), while QLI [based on RLA calculated from Tracing] was 1.48 ± 0.12 (range: 1.09 – 1.67).

Table-1. Sonographic Parameters of Lung Maturity in Included Women

Lung-to-Liver Echogenicity **Hypodense** **Isodense** **Hyperdense** **Marked Hyperdense**	81 (27%) 107 (35.7%) 62 (20.7%) 50 (16.7%)
AFFFP **Present** **Absent**	211 (70.3%) 89 (29.7%)
AFFFP (mm) **Range** **Mean ± SD**	0.2 – 3.4 1.79 ± 0.81
DFE **Present** **Absent**	241 (80.3%) 59 (19.7%)
DFE (mm) **Range** **Mean ± SD**	0.2 – 9.5 5.15 ± 2.83

Table-2RLA and QLI in Included Women

	Range **Mean ± SD**	**MPD** **(95% CI)**	***P****
RLA [calculated from Perpendicular Longest Diameters] (mm^2) **Range** **Mean ± SD**	1066 – 2955 2084.71 ± 579.2	632.35 (605.36 to 659.33)	<0.001 HS
RLA [calculated from Tracing] (mm^2) **Range** **Mean ± SD**	790 – 2066 1452.37 ± 345.56		
QLI [based on RLA calculated from Perpendicular Longest Diameters] **Range** **Mean ± SD**	1.46 – 2.45 2.11 ± 0.26	0.63 (0.61 to 0.64)	<0.001 HS
QLI [based on RLA calculated from Tracing] **Range** **Mean ± SD**	1.09 – 1.67 1.48 ± 0.12		

There were significant paired differences between RLAs and QLIs calculated from perpendicular longest diameters and those calculated from tracing; with the former values being higher than the latter values [mean paired differences 632.35 mm2, 95% CI (605.36 to 659.33), p<0.001; and 0.63, 95% CI (0.61 to 0.64), p<0.001; respectively].

Of the 300 cases, 152 (50.7%) had vaginal delivery and 148 (49.3%) had caesarian delivery. The mean birth weight in neonates of the included women was 2177.5 ± 1239.1 g (range: 850 – 4550 g), 156 (52%) of the neonates were males while 144 (48%) were females.

Neonatal outcome was evaluated, 130 (43.3%) were normal, 44 (14.7%) had TTN, 63 (21%) had

RDS, 10 (3.3%) had BPD and 53 (17.7%) had neonatal mortality.

For the purpose of statistical analysis studied sonographic parameters were associated with adverse neonatal outcome (defined as TTN, RDS, BPD or mortality), serious adverse neonatal outcome (defined as RDS, BPD or mortality), and serious adverse respiratory outcome (defined as RDS or BPD).

Each of AFFFP, DFE, RLA and QLI in included women were significant good predictors of adverse neonatal outcome, as indicated by the significant large AUC [p<0.001]. The best cutoff value of AFFP was 1.85 mm [sensitivity 81.40%, specificity 70.8%, PPV 78.40%, NPV 74.20%]. The best cutoff value of DFE was 5.05 mm [sensitivity 81.40%, specificity 81.50%, PPV 85.20%, NPV 76.80%]. The best cutoff value of QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.28 [sensitivity 80%, specificity 78.50%, PPV 82.90%, NPV 75%]. The best cutoff value of QLI [based on RLA calculated from Tracing] was 1.55 [sensitivity 81.4%, specificity 66.90%, PPV 76.40%, NPV 73.70%].

Each of AFFFP, DFE, RLA and QLI in included women were significant good predictors of serious adverse neonatal outcome, as indicated by the significant large AUC [p<0.001]. The best cutoff value of AFFP was 1.45 mm [sensitivity 87.50%, specificity 78%, PPV 74.30%, NPV 89.50%]. The best cutoff value of DFE was 3.65 mm [sensitivity 87.50%, specificity 85.10%, PPV 80.90%, NPV 90.20%]. The best cutoff value of QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.21 [sensitivity 87.5%, specificity 86.30%, PPV 82.10%, NPV 90.40%]. The best cutoff value of QLI [based on RLA calculated from Tracing] was 1.51 [sensitivity 87.5%, specificity 86.30%, PPV 82.10%, NPV 90.40%].

Each of AFFFP, DFE, RLA and QLI in included women were significant good predictors of serious adverse respiratory outcome, as indicated by the significant large AUC [p<0.001]. The best cutoff value of AFFP was 1.35 mm [sensitivity 82.60%, specificity 76.3%, PPV 52.60%, NPV 93%]. The best cutoff value of DFE was 3.65 mm [sensitivity 82.60%, specificity 80.80%, PPV 57.70%, NPV 93.40%]. The best cutoff value of QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.21 [sensitivity 82.6%, specificity 81.80%, PPV 59.40%, NPV 93.50%]. The best cutoff value of QLI [based on RLA calculated from Tracing] was 1.5 [sensitivity 82.6%, specificity 80.80%, PPV 57.70%, NPV 93.40%].

In order to propose a scoring system for predicting serious adverse respiratory outcome, multiple logistic regression analysis was performed to estimate the weight of association between measured variables and serious adverse respiratory outcome.

According to this logistic regression analysis a scoring system was proposed. ROC curve was performed to estimate the validity of the proposed scoring system in prediction of serious adverse respiratory outcome and showed significant predictability [AUC = 0.822, 95% CI (0.776 to 0.867), p<0.001)].

Table-3. Multiple Logistic Regression Analysis for Estimating the Weight of Association between Measured Variables and Serious Adverse Respiratory Outcome in Included Women

Predictors of Serious Adverse Respiratory Outcome*	OR (95% CI)
Gestational Age	2.03 (0.61 to 6.79)
Sonographic EFW	2.01 (0.75 to 5.38)
Lung-to-Liver Echogenicity	1.19 (0.6 to 2.35)
AFFFP	2.39 (1.09 to 5.22)
DFE	4.35 (1.33 to 14.29)
RLA	3.89 (0.56 to 27.25)
QLI	1.19 (0.19 to 7.51)

Table-4Proposed Scoring System for Predicting Serious Adverse Respiratory Outcome in Included Women

	0	1	2	4
Gestational Age	Very preterm < 32 weeks	Preterm 32 - < 37 weeks	Term ≥ 37 weeks	-
Sonographic EFW	VLBW < 1500 g	LBW 1500 - < 2500 g	ABW ≥ 2500 g	-
Lung-to-Liver Echogenicity	Hypodense/ Isodense	Hyperdense/ Marked Hyperdense	-	-
AFFFP	Absent	-	Present	-
DFE	Absent	-	-	Present
RLA	≤ 2140 mm^2	-	-	> 2140 mm^2
QLI	≤ 2.2	> 2.2	-	-

Total Score 0 – 6 7 – 11 > 11	High risk of serious respiratory morbidity (> 75%) Intermediate risk of serious respiratory morbidity (≅ 20%) Low risk of serious respiratory morbidity (< 5.5%)

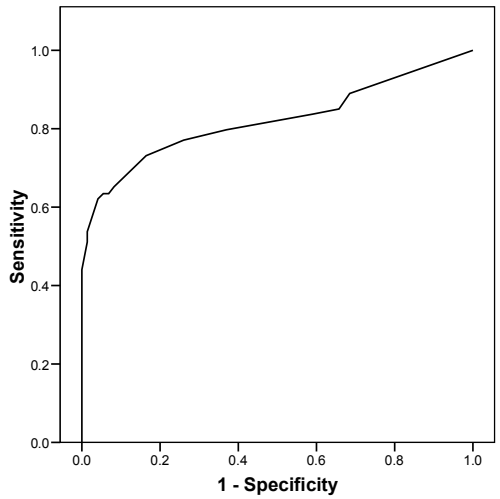

Figure-2 ROC Curve for the Proposed Scoring System for Predicting Serious Adverse Respiratory Outcome in Included Women
AUC = 0.822, 95% CI (0.776 to 0.867), p<0.001

4. Discussion:

Fetal Lung to liver echogenicity was first described by **Bowerman et al., 1984**, who established six categories of lung echogenicity relative to liver, ranging from lung much more echogenic than liver to lung less echogenic than liver. They found a "mature" lung echo pattern in six of seven patients who had L/S values indicative of fetal lung maturity and were cautiously (the total sample size was 11 patients) optimistic that a reproducible relation existed. Subsequently, they suggested that the original six categories might well be condensed into three with little effect on the results.

Conversely, **Cayea et al., 1984**, found echogenicity of the fetal lung of essentially no value in predicting L/S or PG in amniotic fluid. They examined three factors: echogenicity of the lung as compared with liver (essentially as in our study), coarseness of lung echoes as compared with those of liver, and the presence or absence of far-field enhancement through the lung. Theirs was a series of 59 patients who underwent amniocentesis for L/S and PG determinations. Using multiple linear regression analyses, they could demonstrate no predictive value for any of the factors measured as regards fetal lung maturity.

Prakash et al., 2002, studied ratio of fetal lung to liver echogenicity values as possible indices for lung maturity. They classified the images of fetal lung and liver (in the gestational age between 24-38 weeks) into mature lung (reduced pulmonary risk) and immature lung (possible pulmonary risk). The classification had an accuracy ranging from 73%to 96% for prediction of mature lung which is similar to our sudy where 76% of cases having hyperdense lungs have no adverse neonatal outcome.

Similar results were also obtained by **Tekesin et al., 2004**, who studied the relation between lung to liver echogenicity and fetal lung maturity. The ratio of lung to liver >1 (i.e.; more echogenic lung than liver) was found in 65% of patients and was similar to that of maturity levels of standard tests.

When lungs become mature so, the ratio of the volume of the central cavity containing fluid to the total volume of the sphere increases with maturity. This formed the basis of the hypothesis that clinical ultrasound should be able to detect increase in fluid content by demonstrating enhanced sound transmission through fetal lungs **(Tekesin et al., 2004).**

Bree, 1978, reported sonographic identification of free-floating particles (FFPs) about 2-3 mm in size in amniotic fluid of two women at 39 and 40 week gestation. These particles might represent flakes of fetal vernix in the amniotic fluid and he theorized that the presence of these particles may be used as a mark of fetal maturity.

Our results are in agreement with **Gross et al., 1985**, prompted study on 135 women between 34-42 week pregnancy FFPs were present in 39 and absent in 96. when FFPs were present the L/S ratio was mature in 74% of patients and there was increased FFPs in association with large gestational age (LGA) infants.

Conversly, **Hadlock, 1985**, reported that, there have been fetuses with FFPs in amniotic fluid who had immature lung profiles at amniocentesis, and the author therefore, cautioned against the use of this finding in evaluation of fetal lung maturity.

Its also in agreement with **Adair et al., 1995,** studied amniotic fluid turbidity is a predictor of fetal lung maturity when compared with fluorescence polarization assay, it had 91% positive and 87% negative predictive value. Visual inspection of amniotic fluid may be of value in areas where sophisticated methods are unavailable.

Another similar results were obtained by **Shankar and Sandhya, 2010**, who aimed to correlate echogenic amniotic fluid particle size (AFPS) in late third trimester to fetal lung maturity and amniotic fluid optical density (AFOD) at labor. AFPS were measured with specified criteria by real time transabdominal USG (3.5MHz). AFPS was correlated to AFOD value at spontaneous labor in 123 women. Serial AFPS estimation predicts fetal maturity and onset of labor. Fetal lung maturity is followed by AFOD surge culminating in the onset of labor. AFOD which can be measured serially in terms of AFPS serves as a marker for labor and also predicts RDS. This basic knowledge about AFOD and simple cost effective noninvasive

methodology can be used for programming and optimizing labor, and improve perinatal outcome.

The main fetal ossification centers appear ultrasonically as egg-shaped echo rich areas. **Gentilli et al., 1984**, evaluated 312 normal pregnancies between 20 and 40 weeks of gestation for identification and biometric measurement of the distal femoral epiphyseal (DFE) and proximal tibial epiphyseal (PTE) ossification centers are found at the level of the knee, DFE starts to become visible from the age of 33 weeks gestation and it was seen in 94.5% of normal pregnancies from 34 weeks till term. From 36 weeks, the PTE was detectable at the knee level, and it was seen in 87.6% of normal pregnancies from 37 weeks until term. They concluded that sonographic evaluation of fetal ossification centers can accurately assess gestational age in the last weeks of pregnancies.

Our results are in agreement with **Tabsh, 1984**, who demonstrated a mature L/S ratio in 100% of cases in which the PTE was ≥ 5 mm in diameter and DFE ≥ 5 mm in mature L/S ratio in 95% of cases.

Also in agreement with **Goldstein et al., 1988,** who performed a prospective sonographic evaluation of the distal femoral and proximal tibial ossification centers in 228 normal pregnant women which was carried out from 28-40 weeks gestation, DFE & PTE enables the prediction of gestational age during the third trimester with a high degree of accuracy a period in which standard fetal biometric of gestational age including: BPD, AC, limb length measurements are least accurate.

The same results were obtained by **Nazário et al., 1993**, who performed ultrasonographic examinations performed on 1000 pregnant women between the 28th and 40th weeks of gestation who had been seen at a private clinic, all women was known last menstruation, and none had obstetrical or clinical-surgical complications, all were singleton pregnancies, and cases of fetal malformation were excluded from the study. The proximal humeral epiphyseal ossification center was visualized significantly frequently after the 38th week ($P < 0.001$). its specificity was elevated (99%).

Another similar results by **Donne et al., 2005,** who enrolled women with singleton pregnancies of 30-40 weeks gestation in prospective study. The distal femoral, proximal tibial, and proximal humeral ossification centers were identified and measured. A nomogram of fetal bone development was created using the sum of the three diameters. Gestational age correlated well with the diameters of the DFE & PTE centers but even better with the sum of the three ossification centers. Positive predictive values of the fetus having gestational age of at least 37 weeks when the sum of the three centers was 7, 11, and 13 mm were 82%, 94%, and 100%, respectively.

Also in agreement with **Butt and Lim, 2014,** who found the presence of distal femoral epiphysis has a PPV of 96% for indicating a pregnancy of at least 32 weeks, the proximal tibial epiphysis has a PPV of 83% for indicating a pregnancy of at least 37 weeks, and the proximal humeral epiphysis has a PPV of 100% for indicating a pregnancy of at least 38 weeks.

The ossification centers appeares after 31st week gestation. The order of appearance is DFE, PTE and PHE as first, second and third respectively. At first the average size of Distal Femoral Epiphysis was more than Proximal Tibial and Proximal Humeral Epiphysis but on reaching at a menstrual age of 38-39 weeks, the size of epiphysis become almost same. This shows that the proximal humeral epiphysis is growing at a faster pace as compared to proximal tibial and distal femoral epiphysis. So, the size and appearance of these epiphyseal centers will be helpful to determine the gestational age and viability of the fetus in normal as well as medico legal cases. It can also be drawn from the conducted studies that the identification and measurement of these ossification centers may be less affected by fetal growth restriction or excessive growth than other anthropometric ultrasonographic measurements like Crown Rump Length, Abdominal Circumference, etc. **(Kumari et al., 2015)**.

Peralta et al., 2005, aimed to establish reference intervals with gestation for the right and left lung areas and lung area to head circumference ratio (LHR). This was a cross-sectional study of 650 normal singleton pregnancies at 12–32 weeks of gestation. They measured the left and right lung areas on the crosssectional plane of the thorax, used for examination of the four-chamber view of the heart, by three different techniques: firstly, manual tracing of the limits of the lungs; secondly, multiplication of the longest diameter of the lung by its longest perpendicular diameter; thirdly, multiplication of the anteroposterior diameter of the lung at the mid-clavicular line by the perpendicular diameter at the midpoint of the anteroposterior diameter.

They have similar results to those in our study regarding significant difference in measurement of RLA by manual tracing and longest perpendicular diameters. They concluded that the respective mean left and right lung areas (manual tracing) increased with gestational age, from 36 and 58 mm2 at 12 weeks to 220 and 325 mm2 at 20 weeks and 594 and 885 mm2 at 32 weeks. The most reproducible way of measuring the lung area was by manual tracing of the limits of the lungs and the least reproducible was by multiplying the longest diameter of the lungs by their longest perpendicular diameter. Furthermore, the method employing the longest diameter, compared with the tracing method, overestimated both the left and the right lung areas by about 45% and the method

employing the anteroposterior diameter overestimated the area of the right lung by about 35%, but not that of the left lung **(Peralta et al., 2005)**.

Simple multiplication of two perpendicular diameters to calculate an area assumes that the shape is rectangular. However, this is not the case for either the left or the right lung, in the transverse plane of the fetal thorax at the level of the four-chamber view of the heart. Thus, for measurement of the lung area they recommend manual tracing of the limits of the lungs rather than multiplication of lung diameters **(Peralta et al., 2005)**.

Britto et al., 2014, aimed to establish reference ranges for 2-dimensional sonographic measurements of fetal lungs from longitudinal data. A total of 214 fetal lung measurements were longitudinally evaluated in 62 healthy fetuses between 20 and 36 weeks' menstrual age. Both right and left lung areas were measured in the heart 4-chamber view using lung area tracing and axis diameter methods. Multilevel modeling was used to evaluate the expected values and variability with respect to menstrual age and to generate reference ranges for the lung area, lung to-head ratio, quantitative lung index, and observed-to-expected lung-to-head ratio for both lungs.

Britto et al., 2014, provided reference ranges from 20 to 36 weeks of menstrual age, whereas **Peralta et al., 2005** evaluated healthy fetuses from 12 to 32 weeks, although there is less clinical applicability in evaluating lung size before 20 weeks. While in our study we evaluated fetuses from 28 to 42 weeks. Our results are very close to those obtained by **Britto et al., 2014.** However studied range by **Peralta et al., 2005** have only the range from 28 to 32 weeks in common.

Quintero et al., 2011, sought to develop a gestational age–independent sonographic parameter to characterize lung growth. A new index, the quantitative lung index (QLI) was derived using published data on HC and the area of the base of the right lung. Mathematical relationship between RLA and HC was then analyzed. A new parameter of right lung growth was derived from this analysis. No human subjects were involved in this research.

Their data showed that the mean QLI has a relatively constant value of approximately 1.0 between 16-32 weeks. This suggests that the QLI can be used as a sonographic parameter of right lung growth independent of gestational age. This results from dividing 2 quadratic polynomial equations, instead of polynomials of different order. Their data showed that dividing right LA by the square of the HC (QLI) is associated with a relatively constant relationship throughout gestation, which is truly virtually independent of gestational age **(Quintero et al., 2011)**.

Although the mathematical model used to derive the QLI shows a relatively tight confidence interval, the variability of the measurement would need to be tested clinically. The most important advantage of the QLI is its relative stability over a wide gestational age window. This could allow assessment of fetal right lung size and classification of patients as high risk or low at any point during the second trimester, which could facilitate clinical decisions. Because the QLI is relatively constant, and it is easy to calculate mathematically [LA/(HC^2)/100], the diagnosis of a normal QLI can be made at the bedside **(Quintero et al., 2011)**.

Our results were different from those obtained by **Quintero et al., 2011.** QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.11 ± 0.26 (range: 1.46 – 2.45), while QLI [based on RLA calculated from Tracing] was 1.48 ± 0.12 (range: 1.09 – 1.67).

There were significant paired differences between RLAs and QLIs calculated from perpendicular longest diameters and those calculated from tracing; with the former values being higher than the latter values [mean paired differences 632.35 mm2, 95% CI (605.36 to 659.33), $p<0.001$; and 0.63, 95% CI (0.61 to 0.64), $p<0.001$; respectively].

Ruano et al., 2013, aimed to estimate the accuracy of the quantitative lung in isolated congenital diaphragmatic hernia in comparison to other available prediction models. They prospectively evaluated 108 fetuses with isolated (82 left-sided and 26 right-sided) congenital diaphragmatic hernia. The quantitative lung index and observed-to-expected contralateral lung area were measured and compared to the neonatal survival rate and severe postnatal pulmonary arterial hypertension. Overall neonatal mortality was 64.8% (70 of 108). Severe pulmonary arterial hypertension was diagnosed in 68 (63.0%) of the cases, which was associated with neonatal death ($P <.001$). Quantitative lung index was significantly associated with neonatal survival and pulmonary arterial hypertension ($P <.001$), with accuracy to predict survival of 70.9%, and accuracy to predict hypertension of 78.7%. The results are similar to ours as a QLI have the ability to detect adverse neonatal outcome sensitivity 80%, specificity 78.50%, PPV 82.90%, NPV 75%.

Britto et al., 2014, aimed to establish reference ranges for 2-dimensional sonographic measurements of fetal lungs from longitudinal data. Multilevel modeling was used to evaluate the expected values and variability with respect to menstrual age and to generate reference ranges for the lung area, lung to-head ratio, quantitative lung index, and observed-to-expected lung-to-head ratio for both lungs. Their results regrding RLA measured by longest diameters

and tracing mrthodsand also for QLI are close to our results.

Illescas et al., 2016, studied the performance of QLI to predict survival in fetuses with CDH. Observational retrospective study of fetuses with isolated CDH. They followed 31 fetuses with isolated CDH. The mean QLI was 0.66 (95% CI: 0.57–0.75) for survivors and 0.41 (95% CI: 0.25–0.58) for non-survivors ($p < 0.01$). All operated fetuses ($n = 12$) had a QLI <0.5 and none of them survived when the QLI was <0.32. When separately considering the prenatal surgery status, the mean values of the QLI were still significantly different between survivors and non-survivors. The comparative ROC curves showed a better performance of the QLI for the prediction of survival, especially in the group of operated fetuses. Compared to our results it included a small number of cases and the study was on CDH and including results of prenatal surgery, the QLI values were significantly different as our results showed that QLI [based on RLA calculated from Perpendicular Longest Diameters] was 2.11 ± 0.26 (range: 1.46 – 2.45), while QLI [based on RLA calculated from Tracing] was 1.48 ± 0.12 (range: 1.09 – 1.67).

Limitations:

Regarding inclusion criteria, one of the difficulties was meeting all the inclusion criteria especially regarding receiving steroids.

The major difficulty was neonatal assessment as not all cases are admitted to same center. So many cases were excluded due to inability to obtain neonatal outcome. Also there were different protocols for management in different incubators and other factors affecting neonatal outcome as use of surfactant or availability of equipment as ventilators.

Also there's limited trials that tested QLI. Most of these are targeted for congenital diaphragmatic hernia.

Conclusion:

As the most common cause of mortality and neonatal morbidity in preterm and early term fetuses is lung immaturity. The prediction of lung maturity by noninvasive ultrasound methods has been extensively explored.

A new index, the quantitative lung index (QLI) was derived using HC and the area of the base of the right lung. The current study was clinical evaluation of Quantitative Lung Index. QLI = Right lung area/(HC/10)^2. The mean QLI was 2.11 ± 0.26.

Multiple logistic regression analysis was performed to estimate the weight of association between measured variables and serious adverse respiratory outcome and showed significant predictability [AUC = 0.822, 95% CI (0.776 to 0.867), $p<0.001$)].

There were limited number of studies that have clinically validated QLI, some of them were with small number of cases and targeted mainly for cases of CDH. So results have significant variation. This may be also due to no standardized method for measuring RLA which affects QLI values.

So further studies should be performed using more number of cases, different ethnic groups.

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