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Validity Of Magnetic Resonance Imaging In Assessment Of Fetal Lung Maturity in High Risks Pregnancy

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Original Article

Abstract

Background: *Lung function at birth is a combination of at least 3 factors: proper central nervous system function in the respiratory centers, adequate pulmonary blood flow and surfactant. Neonatal respiratory distress syndrome affects 1% of all live births. Magnetic resonance imaging has also been used to assess fetal lungs. Echo-planar Magnetic resonance imaging has been used to quantify lung volume cross-sectionally in abnormal pregnancies*

Objective: *To assess validity of MRI in estimation of fetal lung maturity and compare it with ultrasound grades of lung maturity.*

Methods: *A prospective cross-sectional study, conducted at the Department of Obstetrics and Gynecology in Al-Imamain Al-Khademain Medical City, from 1st of November 2020 to 1st November 2021, in which 30 patients were enrolled in this study.*

Results: *: current study shows that 14 (46.7%) of Neonates were admitted to the neonatal care unit, while 16 (52.3%) were not admitted. Apgar score ≤ 5 was found in 8 (26.3%) of Neonates, while Apgar >5 found in 22 (73.3%) of Neonates. Early neonatal death occurred in 1 (3.3%) and severe respiratory distress occurred in 9 (30.0%) of neonates. mean of lung-to-liver signal intensity ratio (LLSIR) in sever Respiratory distress syndrome, Neonates (RDS) Neonate (1.6 ±0.4), while LLSIR in Neonates with non-sever RDS was (2.3±0.2) with highly significant difference (P<0.001).*

Conclusions: *There was a significant reduction in mean of lung-to-liver signal intensity ratio (LLSIR) in RDS infant (1.6 ±0.4) than those with non-RDS.*

Keywords: *Magnetic Resonance Imaging, Fetal Lung Maturity, Respiratory distress syndrome, Neonates*

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1. INTRODUCTION

Early delivery because of fetal and maternal health concerns is steadily increasing in obstetric practice. The rate of preterm births (before 37 weeks' gestation) increased to more than half a million, or 12.8% of all births worldwide. An estimated 15 million babies are born prematurely every year. That is more than 1 in 10 babies. Approximately 1 million children die each year due to complications of preterm birth. Many survivors face a lifetime of disability, including learning disabilities, visual and hearing problems. Globally, prematurity is the leading cause of death in children under the age of 5 years. And in almost all countries with reliable data, preterm birth rates are increasing (1). According to data published by the Quint-Boenker Preemie Survival Foundation, infant survival is significantly dependent on gestational age at birth. For example, for infants born at 32–33 weeks, the survival rate is 98%, compared with those born at 25 weeks, who have a 50% survival rate (2,3).

Fetal Lung Maturity:

Definition: The development of the human lung is a highly regulated process that begins at just 3 weeks of gestation and continues through 8 years of age. The final stages of development prepare the lung for its role as a gas exchange organ.

Stages of FLM:

The development of the fetal lung is divided into five stages (4):

1. Embryonic covering the period up to 7 weeks.
2. Pseudoglandular covering the period 7–16 weeks.
3. Canalicular covering the period 16–25 weeks.
4. Saccular covering weeks 25–36.
5. Alveolar covering weeks 36-38.

It is usually at the end of the Canalicular stage that epithelia differentiation occurs, with type II pneumocytes differentiating to type I and lamellar bodies (in which surfactant synthesis begins by 20 weeks) forming in type II pneumocytes. By the end of this period, the preterm lung is potentially viable (4). Lung function at birth is a combination of at least 3 factors: proper central nervous system function in the respiratory centers, adequate pulmonary blood flow, and surfactant. Respiratory compromise presenting shortly after birth secondary to a deficiency in pulmonary surfactant is referred to as neonatal respiratory distress syndrome (RDS). Neonatal

RDS affects 1% of all live births, but neonates with RDS are almost always premature (5). Between weeks 24 and 38 of gestation, alveolarization begins to occur at the terminal branches of the developing lung and type II pneumocytes start producing pulmonary surfactant, a lipoprotein mixture that regulates surface tension at the air–liquid interface (6). The presence of amniotic fluid is critical to the development of fetal lungs especially for the 2nd and 3rd stages. An hydramnios before the 20th week of gestation is associated with pulmonary hypoplasia that is unlikely to support extra-uterine survival, but when it occurs after the onset of surfactant production, the lungs may be able to support the neonate (7).

Magnetic Resonance Imaging: Magnetic resonance imaging (MRI) has also been used to assess fetal lungs. Echo-planar MRI has been used to quantify lung volume cross-sectionally in abnormal pregnancies. Researchers used Echo-planar MRI to assess fetal lung growth during pregnancy and related it to amniotic fluid volume(8, 9). While they suggested that the changes demonstrated with this technique could be useful in monitoring the effects of corticosteroids on changes in fetal lung volumes it has not been routinely applied in clinical settings to assess lung maturity prior to delivery or indeed been used to evaluate its usefulness in predicting RDS(8,9). Quantitative and qualitative evaluation of fetal lungs using MRI has however, been shown to be useful in identify fetuses with pulmonary hypoplasia. Osada et al, concluded from their studies that “there is the need for future prospective studies of the use of MRI images to predict severe respiratory disturbance in patient subgroups with specific intrathoracic congenital diseases such as diaphragmatic hernia and oligohydramnios”. Despite these suggestions, this approach has not been applied in clinical practice to assess fetal lung maturity to help in planning delivery of high-risk pregnancies (10).

2. PATIENTS and METHODS

A prospective cross-sectional study, conducted at the Department of Obstetrics and Gynecology in Al-Imamain Al-Khademain Medical City, from 1st of November 2020 to 1st November 2021. All cases admitted to the ward of Obstetric in Al-khademian hospital were due to obstetrical complications. Because of maternal and fetal compromise decisions of delivery and pregnancy termination within 24 hours were taken by seniors’ obstetricians.

Cases included in this study were classified as high risks pregnancies (9 of them are PE, 6 were preterm labor, 5 were uncontrolled GDM, 6 were adherent placenta, and 4 were IUGR)

Inclusion Criteria:

1. High risk pregnancy ladies.
2. Mother age between 16-38 years.
3. GA: 28 -36 weeks+6 days.
4. Claustrophobia and pace maker.
5. single viable fetus

Exclusion Criteria: Claustrophobia, corticosteroid administration, Fetal renal anomaly, IUD, diaphragmatic hernia, oligohydramnios, abnormal liver.

Method: U/S examinations were done to all women for estimation of gestational age and U/S criteria of placental grade of maturity and calcification were recorded depending on radiological reports. As late U/S are not completely reliable for correct estimation of gestational age, we relied on LMP (last menstrual period) and early US. Patients MRI examination were done in Al-khademian hospital training center and image received at workstation. Patients admitted for MRI room, lied in supine or oblique position, no contrast or sedation was given.For intra-subject comparison, LLSIR (Lung Liver Signal Intensity Ratio) was used. Because of its proximity to the lung and its homogeneity, we chose the liver as a reference organ in this study. The signal intensities of the fetal lung and liver were measured on T2-weighted images, and LLSIR (Lung Liver Signal Intensity Ratio) was calculated to measure the fluid content of the fetal lung. MRI was performed in all fetuses with 1.5 T superconductive units (Magnetom Vision, Siemens, Erlangen, Germany and AVANTO, Siemens, Erlangen, Germany) using a phased-array surface coil. After obtaining the horizontal preview of maternal pelvis, half-Fourier acquisition single-shot turbo spin-echo sequences (Magnetom Vision: repetition time (TR) 1000ms, echo time (TE) 64ms, field of view (FOV) 350mm, slice thickness 6mm, matrix 256×112, flip angle 120° and AVANTO: TR 1200ms, TE 64ms, FOV 300mm, slice thickness 5mm, matrix 256×179, flip angle 120°) were oriented in transverse, sagittal, and coronal planes based on the fetal position.

We selected the ideal slice in which both the lung and liver were included. In this slice, an ROI (region of interest) was placed within the homogenous portion of the lung and liver and drawn on a single image of the fetal lung and liver and made as close as possible to 2 cm in diameter. The ROIs were drawn to include the maximum amount of tissue without including organ

borders or vasculature. The ROIs were placed a similar distance from the surface-receiving coil and away from the fetal heart to reduce motion artifact. All calculations of LLSIR were performed by one examiner to eliminate variations. No cases were excluded due to fetal motion. The cut-off value of LLSIR for predicting respiratory outcome was assessed by means of receiver operating characteristic (ROC) analysis. All subjects in this study were singleton pregnancies, who examined once, we excluded cases that we couldn't get ROI of 2cm.

Cases delivered within 24 hour and followed up at neonatal care unit by measuring Apgar score: 1 min and 5 min post-delivery. Neonates were classified as RDS and non RDS groups depending on their need for long term artificial ventilation > 1 min

Diagnostic criteria for RDS: according to clinical, chest X-ray, blood gases, scoring Downs, respiratory rate, cyanosis, retractions, grunting, and apnea.

Statistical Analysis: All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 23 used in this study. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test used when expected variable was less than 20% of total) and t-test used to compare between two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. In the current study we assess the value of LLSIR in RDS, grades of lung maturity and GA to detect the relation between them, this done by calculating the LLSIR for each of these three variables in all patients. The community medicine specialist did statistical analysis of the study.

3. RESULTS

The mean maternal age was (29.6 ± 3.2) years, mean of the lung-to-liver signal intensity ratio (LLSIR) was (2.39 ± 0.59); At ≤33 wks it was (2.43±066) and at >33 wks it was (2.35±052), mean Apgar score at 1 min was (6.03±0.58) and at 5 min was (6.76±0.92), and mean of gestational age was (33.9 ±3.5) weeks (**Table 1**) .

Among the studied group, 14 (46.7%) Neonates needed admission to NICU, 8 (26.3%) had Apgar score ≤ 5 , 22 (73.3%) neonates had Apgar score >5. Early neonatal death occurred in one (3.3%) neonate and severe respiratory distress occurred in 9 (30.0%) neonates, (**Table 2**)..

A Significant association was found between grades of lung maturity and RDS., (P=0.02),

while no signifciant association was found between grade of lung maturity and admission to NICU, (P>0.05), (**Table 3**).

No significant difference had been found in mean LLSIR across the grade of lung maturity, (P>0.05). A signifciant difference was found in mean LLSIR across the admission to NICU where admitted child had lower LLSIR compared to non-admitted neonates, the mean LLSIR was 1.70 ± 0.20 and 2.29 ± 0.60, respectively, (P<0.001). On the other hand neonates with RDS had significantly lower mean LLSIR compared to those with no RDS, 1.60 ± 0.40 and 2.30 ± 0.20, resepctively, (P<0.001), (**Table 4**).

Furthermore, there was a signifciant direct (positive) correlation between gestational age and LLSIR (**Figure 1**).

The validity of LLSIR to detect the respiratory outcomes was assessed using the reciever operating characteristics (ROC) curve analysis (**Figure 2**) which revealed that at a cut-off value of LLSIR ≤ 2 , the area under the ROC curve (AUC) was 0.90, giving a sensitivity of 100%, specificity 74%, accuracy 88%, negative predictive value (NPV) 100%, and a positive predictive value (PPV) of (71%) , (**Table 5**).

Table 1. Means of different variables in the studied group

Variables		**Mean**	**SD**
Maternal age (years)		29.6	3.2
LLSIR	**≤33**	2.43	0.66
	> 33	2.35	0.52
	Overall	2.39	0.59
Apgar score	At 1 min	6.03	0.58
	At 5 min	6.76	0.92
Gestational age (weeks)		33.9	3.5

SD: standard deviation

Table 2. Neonate outcome in the studied group

		No.	%
Admission to NICU	Yes	14	46.7
	No	16	52.3
Apgar score at 5 min.	≤ 5	8	26.7
	> 5	22	73.3
Neonate outcome	Death	1	3.3
	Alive	29	96.7
Respiratory distress syndrome (RDS)	RDS	9	30
	Non RDS	21	70

Table 3. Relationship of grade of lung maturity with admission to NICU and severity of RDS

Variable		**Grade II**		**Grade III**		**Total**		**P. value**
		No.	**%**	**No.**	**%**	**No.**	**%**	
Admission to NICU	Admitted	8	53.3	6	40.0	14	46.7	0.400
	Not-admitted	7	46.7	9	60.0	16	53.3	
Total		15	100.0	15	100.0	30	100.0	
RDS	RDS	6	40.0	3	20.0	9	30.0	0.020
	No RDS	9	60.0	12	80.0	21	70.0	
Total		15	100.0	15	100.0	30	100.0	

NICU : Neonatal Intensive Care Unit
RDS: Respiratory distress syndrome

Table 4. Differences in LLSIR according to the grades of lung maturity , admission to NICU and severity of RDS

Variable		NO. of neonates	Mean	SD	P. value
Grade	Grade II	19	2.43	0.60	0.600
	Grade III	11	2.35	0.40	
Admission to NICU	Yes	14	1.70	0.20	<0.001
	No	16	2.29	0.60	
RDS	RDS	9	1.60	0.40	<0.001
	No RDS	21	2.30	0.20	

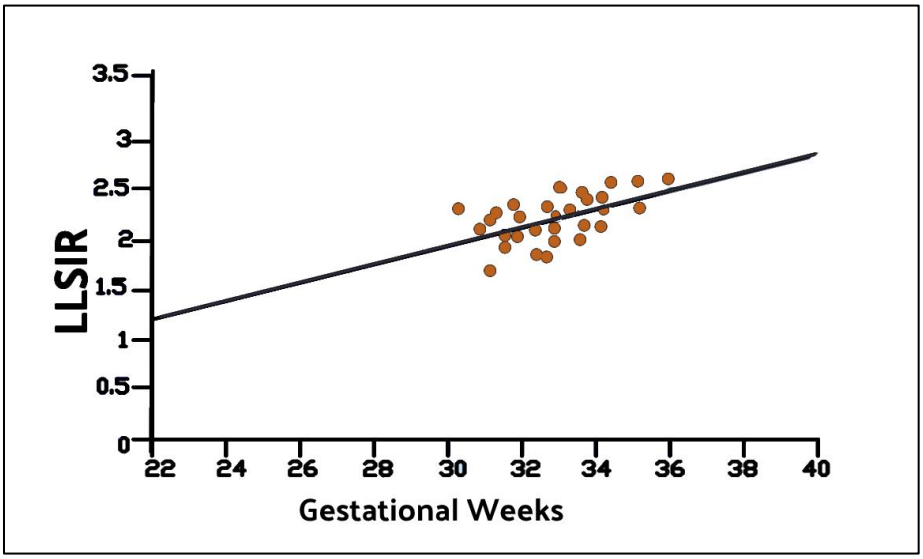

Figure 1. Relationship between LLSIR and gestational weeks

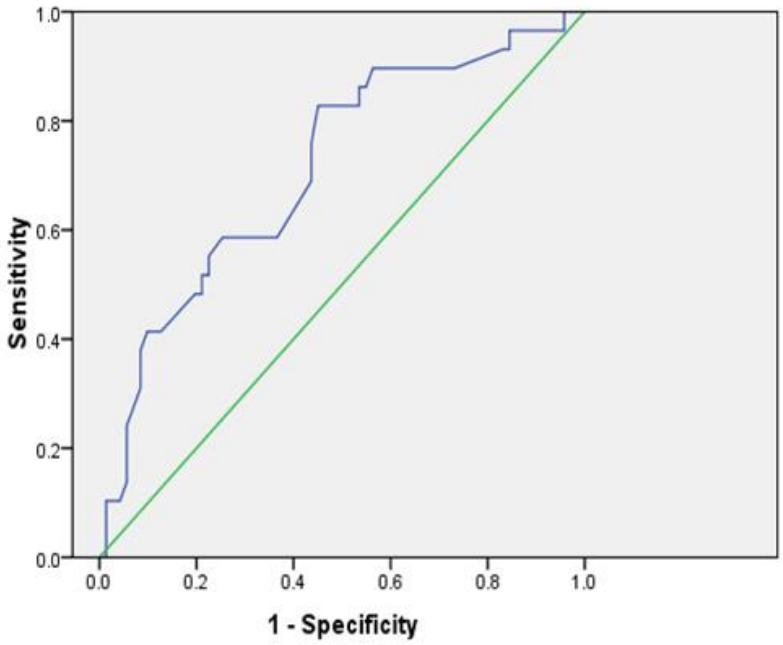

Figure 2. Receiver Operating Characteristics (ROC) curve for LLSIR in RDS group (AUC=0.90)

Table 5. Validity test of LLSIR to detect the respiratory outcome after birth

Cutoff value of LLSIR	≤ 2
Sensitivity	100.0%
Specificity	74.0%
Accuracy	88.0%
NPV	100.0%
PPV	71.0%

4. DISCUSSION

Assessment of fetal lung development based on its SI has been reported in the literature. Ikeda et al (11) and Levine et al (12) found that absolute SI of the normal lungs increases on T2-weighted images and decreases on T1-weighted images throughout gestation. The absolute SI measurements, however, depend on the distance between the structure and the coil and are therefore not consistent between examinations or between types of MRI machines (13). In the current study we used the magnetic resonance image to determine the lung-to-liver signal intensity ratio (LLSIR) and we used this ratio to estimate fetal lung maturity, severe respiratory distress syndrome and the need for NICU admission. The mean maternal age was at third decades, with mean of (LLSIR) was more than 2, same that found by Kuwashima S et al, in a study conducted in 2015 when they diagnosis of pulmonary hypoplasia by using MRI (14). Many studies found an association between lung hypoplasia or gestational age with various types of lung SI measurements (15,16). In the current study there is an association between the increased level of LLSIR with increment of gestational age (GA). This is in agreement with that found by Moshiri M et al, in which they found by using fetal MRI there is a significant linear association between LLSIR and gestational age (17). While in a previous studies carried by Keller et al, examining lung-liver, lung-amniotic fluid, lung-muscle, liver-fluid, and liver-muscle SI single shot fast spin echo ratios in 35 healthy fetuses, found no relationship to gestational age and no clinical relevance for fetal lung SI values; they postulated that liver SI changes with age and thus may not be a suitable reference structure (18). Balassy et al, in a study of 126 normal singleton pregnancies, evaluated SI ratios of lung-liver and lung-gastric fluid for 6 different pulse sequences, did find that fetal liver seemed to be an adequate reference for the investigation of lung maturation and that a T1- weighted sequence was most accurate for the measurement of lung SI (19). Gorincour et al, in a 2009 study of 115 fetuses without lung disease, found an exponential relationship between lung-liver and lung-psoas HASTE ratios with EGA, and a linear relationship with liver signal and EGA, and psoas signal and EGA (20). A 2011 study found intriguing results when 21 singleton pregnancies received antenatal steroid treatment; the lung-liver T2-weighted TSE sequence SI ratios increased significantly between less than 24 hours versus more than 48 hours after betamethasone administration, whereas lung volumes did not change (21).

Recent data suggest that fetuses delivered between 36 and 38 weeks' EGA, even with mature fetal lung development, still have a higher risk of adverse outcome compared with term infants (22, 23). In the present study there is significant difference was found regarding non RDS in grade III of lung maturity (P=0.02) No significant difference found between grade of lung maturity and NICU admission (p=0.4), also no significant difference between grades of lung maturity according to LLISR (P=0.6). Current study mentioned that there is significant increase in LLSIR in the non RDS group than in the RDS group with significant decrease in NICU admission in the former, which is the same that found by Oka et al., in other words, good respiratory function is expected by a high LLSIR. The severe RDS group manifested a low LLSIR throughout pregnancy, yielding a marked difference in signal intensity with the non- severe RDS group at similar gestational ages (24). Perkins et al, study revealed that on the curve to assess the validity of the test to detect the fetal lung maturity, the best cut-off point is generally chosen at the closest point in which specificity = 1 and sensitivity = 1. Using this cut-off value, we can classify all fetuses in disease predicted group and non-disease predicted group (25). Oka et al, identified a cut-off value of LLSIR on ≤2.0 appeared optimal, providing a sensitivity of 100% (or 8/8) (95% CI = 52–100%) and a specificity of 73% (or 22/30) (95% CI = 54–88%) (24).

5. CONCLUSIONS

1. There was a significant reduction in mean of lung-to-liver signal intensity ratio (LLSIR) in RDS infant (1.6 ±0.4) than those with non-RDS.

2. The level of LLSIR was increased with increased gestational age (GA).

3. A cutoff value ≤ 2 can be applied as a suitable screening test for RDS with fair diagnostic performance.

Ethical Clearance:

The purpose and procedures were explained to all participants and they were given the right to participate or not and informed consent was obtained. All information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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