Evaluation of the Relationship Between Fetal Lung to Head Ratio and Amniotic Fluid Index in the Third Trimester of Pregnancy

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ABSTRACT

Background & Objective: This study assessed the relationship between the ratio of fetal lung volume to head circumference and amniotic fluid index (AFI) in the third trimester of pregnancy.

Materials & Methods: This prospective study was performed on low-risk pregnant women in their third trimester of pregnancy. Fetal lung volume was determined separately using the Pearson correlation coefficient between the LHR for both lungs and the lung-to-head ratio (LHR) for the right and left lungs. Moreover, the AFI was evaluated, and the Pearson correlation coefficient between LHR for both lungs and AFI was investigated.

Results: Overall, 112 pregnant women were included in the study. The mean ± standard deviation (SD) of fetal Observed/Expected Right LHR (O/E RLHR) and O/E Left LHR (O/E LLHR) were 113.9±0.36 and 97.13±27.87, respectively. The mean ± SD of AFI was 12.5±4.96 cm. Pearson correlation coefficient did not show a significant relationship between AFI and the left and right LHR (P>0.05). However, O/E RLHR was significantly correlated with abdominal circumference (P=0.02, r=0.2), gestational age (P=0.21, r=0.27), and fetal weight (P<0.001, r=0.27). There was a positive correlation between the number of days the infant was admitted to the neonatal intensive care unit and the volume of the right lung of the fetus (P=0.03, r=0.2). No correlation was observed between fetal parameters and the volume of the left lung of the fetus.

Conclusion: The results of this study showed that AFI in the third trimester of pregnancy was not significantly correlated with LHR.

Keywords: Amniotic fluid index, Lung hypoplasia, Lung to head ratio, Oligohydramnios

Introduction

Pulmonary hypoplasia is found in 7%-10% of neonatal autopsies and up to 50% of cases with other congenital abnormalities (1, 2). The causes of pulmonary hypoplasia are fetal immobility, chest compression, and severe oligohydramnios. There are different pathological definitions for pulmonary hypoplasia, such as decrease in dry lung weight (W/D), lung-to-body weight ratio, number of radial alveoli, and/or lung DNA content (2-4).

One of the factors affecting the growth of fetal lungs is the presence of physical forces. Amniotic fluid is one of the factors that provide this pressure (5). Fluid pressure in the airways and fetal respiratory movements are accepted as a part of normal lung development in humans. Amniotic fluid volume varies from week to week and increases for up to 39 weeks, followed by a decline. The average volume of amniotic fluid in the third trimester of pregnancy is 700-800 mL (6).
The premature rupture of membranes (PROM) and renal failure due to amniotic fluid depletion (oligohydramnios) are accepted as the leading causes of limited lung growth (7). PROM is the rupture of the amniotic sac before 37 weeks of gestation (8). Exposure of the fetus to severe oligohydramnios during the critical periods of pregnancy (i.e., approximately 20-22 weeks) may lead to pulmonary hypoplasia (5, 9). However, the main mechanism of respiratory problems and pulmonary hypoplasia by oligohydramnios is not fully understood (5, 10). There is insufficient information regarding the relationship between fluid volume loss and pulmonary hypoplasia in the late second or early third trimesters of pregnancy. In addition, available data about the severity of oligohydramnios associated with adverse respiratory consequences is limited (11). Studies have shown that diminished amniotic fluid volume is associated with postpartum respiratory morbidity (12).

Amniotic fluid volume is an effective factor in fetal lung growth. Therefore, we hypothesized that amniotic fluid depletion is associated with decreased lung growth, and perhaps, measuring amniotic fluid volume can predict fetal lung growth status. Various methods have been proposed to examine the fetal lung volume, one of which is measuring the surface area of the lungs relative to the head circumference (LHR) using two-dimensional ultrasound (13-15). In this technique, LHR is calculated by dividing the largest vertical diameter of the lungs in the four-chamber view of the heart by head circumference (Figure 1). Several studies have reported an improvement in neonatal survival with elevation in the LHR (16). Consequently, this study was designed to determine the relationship between lung volume to fetal head circumference ratio and AFI in the third trimester of pregnancy.

Figure 1. Lung to head ratio (LHR) is calculated by dividing the lungs’ largest vertical diameter by the heart’s four-chamber view by head circumference.

Materials and Methods

This cross-sectional study with the ethics code of IR.TUMS.IKHC.REC.1400.159 was performed on healthy pregnant women referring to Imam Khomeini Hospital, Tehran, Iran, during September 2020-September 2021 for routine pregnancy care. The inclusion criteria comprised of the gestational age of 34-41 weeks based on the last menstrual period or first-trimester ultrasound, singleton pregnancy, and low-risk pregnancy. The exclusion criteria included fetal malformation, abnormal presentation, and a history of premature infant death.

In the current study, high-risk pregnancies were chronic diseases (e.g., diabetes, hypertension, heart disease), maternal malnutrition, pregnancy under the age of 18 or over 35, weight less than 45 kg, maternal height shorter than 150 cm, short interval between pregnancies (gestation interval less than one year), preeclampsia, placental abruption, fetal intrauterine growth retardation, underlying maternal diseases before and during pregnancy, addiction, history of pregnancy problems, Rh incompatibility in pregnancy, pregnancy with in vitro fertilization or assisted reproductive technologies and other manipulations, and exposure to teratogenic medications.

After reviewing the inclusion criteria for those eligible to enter the study, the method and purpose of the research were explained to the participants, and if they were willing to participate in the study, written informed consent was taken. Next, one of the researchers completed a checklist containing items on demographic information, such as maternal age, height, pre-pregnancy weight, current pregnancy information, fertility information, and a history of maternal diseases. Afterward, the participants underwent ultrasonography (PHILIPS Affiniti 50) to determine the amniotic fluid volume and lung volume. A perinatologist performed all ultrasound examinations.

In addition, the first five measurements made by the researchers were reviewed by another evaluator to assess compliance with the protocol. Lung volume was determined using LHR for the right and left lungs separately. The longest two lines perpendicular to each other on the surface of the view of the four cavities of the heart in a transverse scan of the fetal chest were measured and multiplied. Then, the obtained value was divided by head circumference by entering the numbers obtained at https://perinatology.com/calculators/LHR.htm.

Lung area: length1×length2

The Lung-to-Head Ratio (LHR) = Lung area/Head circumference

O/E LHR= (Observed LHR/Expected LHR)×100

Fetal growth is assessed using fetal parameters, such as biparietal diameter, head circumference, abdominal...
circumference (AC), and femoral length. The expected fetal weight (EFW) was estimated using embryonic parameters and SonoCare software as grams and percentages to obtain gestational age. To specify the volume of amniotic fluid, the amniotic fluid index (AFI) was determined. The AFI is equal to the sum of the single deepest pockets of each quarter of the uterus. To assess whether AFI is normal, the values of the percentile reference range specific to gestational age were used.

At the age of 34–41 weeks, amniotic fluid volumes <5, 5–8, and >8 cm were considered oligohydramnios (2.5%), borderline (2.5%–50%), and normal (above 50%), respectively. Lung volume was compared and evaluated accordingly (17). During the ultrasound evaluation, high-risk embryos identified according to the standard protocol were followed up. The variables studied in this study included LHR for the right and left lungs of the fetus and the relationship of AFI with these two factors.

Statistical Analysis
For quantitative data, mean and SD were used, and for qualitative data, numbers and percentages were reported. First, the normality of data distribution for all quantitative variables was examined by the Kolmogorov-Smirnov test. This test showed that the distribution of data was normal. As a result, the relationship between the quantitative variables was examined by the Pearson correlation coefficient (r). This test demonstrated the strength and direction of the linear relationship between two continuous variables (correlation between E/O LLHR and E/O RLHR with AFI, gestational age, PROM and AC%). To determine whether the correlation between variables is significant, we compared the p-value to a significant level (P<0.05). The t-test examined the difference in lung volume of the subgroups.

Results
In this study, 112 pregnant women were included. The mean±SD of the age of the participants and gestational age at the time of enrollment were 30.17±5.45 years and 35.98±1.59 weeks, respectively (Table 1). During the study, nine (8%) patients had PROM and nine (8%) infants were admitted to the Neonatal Intensive Care Unit (NICU) after birth with a mean hospitalization of 3.45±2.5 days.

Table 1. Demographic characteristics of participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>30.17±5.45</td>
</tr>
<tr>
<td>Gestational age (mean±SD)</td>
<td>36.06±1.68</td>
</tr>
</tbody>
</table>

Ultrasound results are shown in Table 2. Based on the ultrasound, the mean±SD of estimated fetal weight was 2829.35±530.88 g. Moreover, 10 (8.1%) cases had growth retardation with AC less than 10% or EFW less than 10%. The mean±SD of AFI was 12.5±4.96 cm. In this study, 18 (16.1%) patients had decreased amniotic fluid volume (AFI<8 cm). Borderline AFI was observed in nine (8%) patients and oligohydramnios in six (5.4%) cases.

The mean Observed Left LHR (OLLHR) and mean±SD Observed Right LHR (ORLHR) were 8.2±0.81 and 3.5±1.2, respectively. According to reference (18), if LHR is less than 1.4, the prognosis is unfavorable. Classification of both right and left lung ratios was performed on this basis. The LHR for the left lung was less than 1.4, but not in the right lung. The means of O/E RLHR and O/E LLHR were 113.9±0.36 and 97.13±27.87, respectively.

In the present study, nine (8%) infants were admitted to the NICU with a right lung volume of 103.47±20.61 and an O/E LLHR of 88.96±22.34. In the non-NICU group, the mean O/E RLH was 114.84±25.99 and the mean O/E LLHR was 97.85±28.28. Statistical analysis did not show a significant difference between the right lung volume (P=0.5) and the left lung volume in these two groups (P=0.4).

Furthermore, the mean right fetal lung volume in pregnancies with PROM was 113.43±29.68, and for the left lung volume, it was 87.48±33.53. On the other hand, in subjects without PROM, the mean O/E RLHR was 113.97±25.5 and the mean O/E LLHR was 97.13±27.87. Our results did not reveal a significant difference between the two groups regarding right lung volume (P=0.45) and left lung volume (P=0.37).

Table 2. Sonographic finding in the participants

<table>
<thead>
<tr>
<th>Fetal estimated weight</th>
<th>2829/35±530.88</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLLHR</td>
<td>2.82±0.81</td>
</tr>
<tr>
<td>ORLHR</td>
<td>5.32±1.22</td>
</tr>
<tr>
<td>O/EL LHR</td>
<td>97.13±27.87</td>
</tr>
<tr>
<td>O/E R LHR</td>
<td>113.9±25.71</td>
</tr>
<tr>
<td>AFI</td>
<td>12.5±4.69</td>
</tr>
<tr>
<td>Maximum vertical pocket</td>
<td>4.48±1.35</td>
</tr>
</tbody>
</table>

The relationships between the studied variables based on the Pearson correlation coefficient are presented in Table 3. Pearson correlation coefficient demonstrated that AFI was not significantly associated with O/E LLHR nor O/E RLHR (P=0.08, r=0.16) and (P=0.4, r=0.07), respectively. Weight percentile had a positive correlation with O/E LHR of the right lung (P<0.001, r=0.27). However, no significant correlation was observed between weight percentile and the left lung volume (P=0.3). Gestational age had a significant positive relationship with the right lung volume (P=0.21, r=0.27). However, gestational age had no significant relationship with the left lung volume (P=0.3). Moreover, AC
percentage had no significant relationship with O/E LLHR ($P=0.75$), but it was significantly correlated with O/E RLHR ($P=0.02, r=0.2$).

In addition, we examined the relationship between the hospitalization days and pulmonary parameters. The number of days hospitalized in NICU was not related to the left lung volume ($P=0.12$). However, it had a significant negative correlation with O/E RLHR ($P=0.03, r=-0.2$) such that there was a significant negative 20% correlation between the number of hospitalization days and the right lung volume. In other words, when this parameter is low, the risk of the hospitalization (days of hospitalization) of the infant increases. PROM was not significantly associated with any of the pulmonary parameters ($P>0.05$).

### Table 3. Correlation between E/O LLHR and E/O RLHR with AFI, gestational age, PROM and AC

<table>
<thead>
<tr>
<th></th>
<th>E/O LLHR</th>
<th>E/O RLHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R Value</td>
<td>P-value</td>
</tr>
<tr>
<td>AFI</td>
<td>0.16</td>
<td>0.083</td>
</tr>
<tr>
<td>AC%</td>
<td>0.03</td>
<td>0.75</td>
</tr>
<tr>
<td>Fetal estimated weight</td>
<td>0.08</td>
<td>0.372</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.09</td>
<td>0.34</td>
</tr>
<tr>
<td>NICU admission days</td>
<td>-0.14</td>
<td>0.12</td>
</tr>
</tbody>
</table>

### Discussion

This study aimed to assess the relationship between AFI and fetal lung volume in the third trimester of pregnancy. We found no significant correlation between AFI and LHR during 34–41 weeks of gestation. Fetal lung fluid balance and fetal respiration are the most important factors required for normal lung growth. Amniotic fluid production is a dynamic process. As a general rule, the earlier severe amniotic fluid depletion is diagnosed, the greater the risk of pulmonary hypoplasia. The early detection of oligohydramnios is considered an indicator of poor pregnancy outcomes (19).

Najrana compared the mice with induced oligohydramnios with those that did not receive any intervention and found that augmented secondary external compression to severe oligohydramnios could compromise cell size and impair epithelial and endothelial growth (9), and play a role in the small size of the lungs. Studies show that decreased amniotic fluid volume in the first half of pregnancy may be correlated with pulmonary hypoplasia. However, no study indicated an association between AFI and lung volume in the third trimester of pregnancy.

In addition, studies showing a relationship between diminished amniotic fluid volume and respiratory distress syndrome (RDS) in the second half of pregnancy have yielded conflicting results. Lajber et al. reported that AFI<5 cm in term pregnancy was associated with fetal distress (20). However, Sahin et al. revealed that the decline in borderline amniotic fluid volume (5.1–8 cm) at 34–36 weeks of gestation was not associated with RDS (21).

One of the main predictors of respiratory function in infants is a sufficient area of gas exchange epithelium. This area is directly related to the fetal lung volume. Although various methods have been used to measure fetal lung volume (22), there is no consensus on the best measurement technique (23). In this study, we used the ratio of lung circumference to fetal head used to diagnose pulmonary hypoplasia.

In 1996, Metkus et al. introduced LHR, which allows indirect assessment of fetal lung volume. Therefore, LHR evaluation indirectly predicts prenatal pulmonary hypoplasia using two-dimensional ultrasound. In 2005, Peralta et al. (23) showed that LHR increased exponentially with age, highlighting the significance of considering gestational age. To date, ultrasonography in anticipation of LHR has proven its value as an independent measure for prognosis in fetuses with CDH (22). A prospective cohort study by Afreen et al. indicated that in preterm infants (30-34 weeks) with RDS, fetal LHR 72 hours before birth was significantly lower than a control group (24).

Furthermore, there was no significant relationship between gestational age and Observed LLHR and O/E LLHR, but there was a significant correlation between gestational age and Observed RLHR and O/E RLHR. As a result, right LHRs rise exponentially with gestational age. Peralta et al. in 2005 observed a significant relationship between the mean left and right lung areas and gestational age (23). In our study, a significant positive correlation was noted between the number of days of hospitalization and Observed RLHR and O/E RLHR. Afreen et al. in 2021 examined LHR as a potential parameter for predicting respiratory distress in infants and found similar results to our study (24).

Pregnancy age, fetal weight estimation, and AC were significantly associated with Observed RLHR and O/E...
RLHR. In addition, AC was significantly associated with Observed LLHR. The results of Ruben et al. (16) were similar to ours. Jani et al., unlike our study, did not show a significant relationship between gestational age and O/E LHR (25). In the current investigation, fetal weight estimation had a significant relationship with Observed RLHR and O/E RLHR, consistent with the findings of Ruano et al. (26).

In the present study, PROM occurred in eight cases; therefore, pregnancy was terminated because the gestational age was over 34 weeks. In this study, 18 (16.1%) patients had decreased amniotic fluid volume (AFI<8 cm), of which borderline AFI was found in nine (8%) cases and oligohydramnios was detected in six (5.4%) cases. Moreover, 10 (8.1%) individuals had growth retardation as AC less than 10% or EFW less than 10%.

According to the literature, low-risk pregnancies can be at risk for amniotic fluid volume disorders, small for gestational age (SGA), and large for gestational age (LGA) pregnancies (27-29). Such that 16% have growth disorders and 15% have disorders of amniotic fluid volume (27), which is in line with the findings of our study.

The current study was performed prospectively. Furthermore, two-dimensional ultrasound was used to determine the fetal lung volume due to the public access to this device, which is one of the strengths of the study. However, the limited sample size was a limitation for this study. At large, we did not find a relationship between AFI and LHR in the third trimester of pregnancy. Factors other than amniotic fluid volume may play a role in fetal lung growth in the third trimester of pregnancy. For example, fetal lung maturation is also affected by fetal kidney function, steroid hormones, glucocorticoids, and androgens (30).

## Conclusion

The results of this study disclosed that AFI in the third trimester of pregnancy was not significantly correlated with LHR. Therefore, it seems that normal AFI alone in low-risk pregnancies does not predict normal fetal lung volume in the third trimester of pregnancy. Future studies are recommended to examine the relationship of AFI with lung volume in high-risk pregnancies in the third trimester of pregnancy.

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## Conflict of Interest

The authors declared no conflict of interest.

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