ROLE OF FETAL PULMONARY ARTERY DOPPLER IN PREDICTING RISK OF NEONATAL RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Introduction: To determine the optimal time to safely deliver a baby prematurely due to various clinical situations, it is crucial to accurately assess fetal lung maturity. Sonography, a non-invasive technique for evaluating fetal lung maturity, can be useful in predicting the risk of developing neonatal respiratory distress compared to amniocentesis, which is an invasive procedure with associated risks. AIM - This study aimed to determine if fetal main pulmonary artery doppler can play a role in predicting the risk of developing respiratory distress syndrome in neonates. Material and Methods: The participants in this prospective cross-sectional study were 75 pregnant women with gestational ages ranging from 34 weeks to 36 weeks +6 days. Ultrasound doppler examination was conducted, peak systolic velocity (PSV), Systolic /Diastolic ratio, pulsatility index, and resistive index were measured, and acceleration time/ejection time ratio was measured and calculated for the fetal main pulmonary artery. The diagnostic accuracy of these values was tested for predicting neonatal respiratory distress. Result: Of the 75 fetuses included in the study, 15 (20%) showed some signs of neonatal respiratory distress syndrome (RDS). The Acceleration time/Ejection time (AT/ET) ratio in fetal pulmonary artery correlated significantly with the development of respiratory distress syndrome in neonates (P=0.001). Fetuses with respiratory distress syndrome had higher Pulsatility Index and Resistive Index values, while their AT/ET ratio was low. AT/ET was found to predict respiratory distress development with a cutoff value of 0.30 (sensitivity: 98.3 percent; specificity: 86.67 percent). Pulsatility Index and Resistive Index displayed lower sensitivity and specificity than AT/ET ratio. Conclusion: The fetal main pulmonary artery AT/ET ratio has high sensitivity and specificity for predicting the development of neonatal respiratory distress syndrome. Thus, we recommend that a fetus with an AT/ET ratio of <0.30 be delivered in a facility with good neonatal care.

KEYWORDS Newborn RDS, Fetal ultrasonography, Pulmonary artery, Antenatal

Introduction

The most common cause of respiratory distress in preterm infants is hyaline membrane disease, often known as respiratory distress syndrome (RDS), linked to both morphological and functional lung immaturity. It is more common in male fetuses and is around six times more likely in children born to diabetic mothers [1]. Every year, roughly a million cases are reported in India [2]. The most significant risk factor for RDS is prematurity [1]. Other risks include maternal diabetes, caesarean birth, male sex, prenatal tobacco usage by the mother and preeclampsia. RDS is caused by a lack of surfactant in the fetus. Surfactant deficiency leads to a reduction in lung compliance and functional residual capacity and an increase in dead space. In addition, 80 percent of cardiac output is lost due to the substantial V/Q mismatch and right-to-left shunt [3,4].
Amniocentesis has been done earlier to evaluate amniotic fluid lamellar body count, the lecithin/sphingomyelin ratio, and the presence or absence of phosphatidylglycerol to measure fetal lung maturity. However, amniocentesis is an invasive technique associated with risks (upto 1%) and complications such as haemorrhage, premature rupture of membranes or early labour [5]. Thus, fetal ultrasound, a non-invasive, very commonly available and safe, must be used more frequently.

As the fetal lungs grow throughout pregnancy, the sonographic echogenicity of the lungs also changes. With increasing gestation, changes occur in the pulmonary vasculature also. There is an increase in the number of pulmonary arteries with a slight decrease in pulmonary arterial vasculature resistance. Fetal doppler evaluation of the main pulmonary artery has been evaluated to predict fetal pulmonary hypoplasia and determine fetal lung maturity. The ratio of acceleration time to ejection time (AT/ET) has been demonstrated to be predictive of the results of immature surfactant/albumin ratios by Mauro H Schenone and others [6], implying that fetal pulmonary artery Doppler can be used to predict lung maturity in the fetus.

GAFA Moety in 2015 found that the AT/ET ratio of the main pulmonary artery can predict the development of respiratory distress in a newborn with good sensitivity and specificity. They suggested that fetuses with an AT/ET ratio of less than 0.305 had a high risk of respiratory difficulty [7].

Our study intended to see if fetal main pulmonary artery (MPA) doppler indices could predict the risk of newborn respiratory distress in late preterm (34 to 36+6 weeks) pregnancies.

Material and Methods

This prospective cross-sectional study was conducted in our institute in the Department of Radiodiagnosis in collaboration with the Department of Obstetrics and Gynecology with a study duration of 2 yrs. Approval of the Institutional Ethical Committee was sought before commencing the study. The study comprised pregnant women who visited the Obstetrics department between 34 and 36+6 weeks of pregnancy, either in active labour or who were admitted for elective caesarean section depending on the clinical scenario. Pregnant women with a history of intake of antenatal steroids, any fetal chromosomal or major structural abnormality diagnosed antenatally, uncertain gestational age, multiple pregnancies, small or large for gestational age fetuses and antenatal haemorrhage were excluded from the study. 75 participants were selected depending on the inclusion and exclusion criteria. Informed consent was obtained from all participants before including in the study.

The fetal pulmonary artery doppler examination was conducted on PHILIPS EPIQ 7G ultrasound machine using the standard convex multiband transducer. A routine antenatal ultrasound examination was performed for all participants to determine the fetal biometry, amniotic fluid, and fetal weight. A comprehensive assessment of the fetal heart was performed to rule out any major anomaly. The fetal main pulmonary artery was examined with the fetus at rest in an axial section. Pulse wave and colour Doppler were used to evaluate the pulmonary artery to obtain the various parameters in its mid portion - Systolic/diastolic ratio, Resistive Index (RI), Pulsatility Index (PI), peak systolic velocity (PSV). Acceleration time (AT- time taken to reach a maximum flow of the peak systolic velocity) and ejection time (ET - period from the start of ventricular systole to the end) were determined from the waveform, and AT/ET ratio was calculated (Fig 1a-c). The average of three measurements was taken for all parameters.

All newborns were followed for the development of any respiratory distress. In addition, the APGAR score of newborns was noted. Newborns with respiratory distress were admitted to the Neonatal Intensive Care Unit and managed as per the clinical situation.

Antenatal fetal main pulmonary artery doppler findings correlated with the neonatal development of respiratory distress syndrome.

Analysis of statistical data

Range, median, frequencies (number of cases), and relative frequencies (percentages) were used to describe the data. A Kolmogorov-Smirnov test was employed to see if the data were normal. Student t-test and Mann-Whitney U test for independent samples for parametric and non-parametric data were used to compare quantitative variables between the research groups. The ROC (receiver operator characteristic curve) was created, and the criteria value was calculated based on specificity and sensitivity. AUC (area under the curve) was calculated. Statistical significance was determined by a probability value (p-value) less than 0.05. SPSS 21version (SPSS Inc., Chicago, IL, USA) was used to do all statistical computations.

Results

In total, 75 fetuses were examined, of which 15 developed respiratory distress. This study included all pregnant females with a singleton pregnancy in late preterm (between 34 and 36+6 weeks), whether in active labour or indicated for elective caesarean delivery.

All patients were submitted to sonography after obtaining informed consent. Following fetal biometry (containing biparietal diameter, head circumference, abdominal circumference and femur length), a focused examination of the fetal heart and pulmonary artery was performed.

Peak systolic velocity (PSV), End diastolic velocity (EDV), Pulsatility Index (PI), Resistive Index (RI) and S/D ratio were evaluated, and AT/ET ratio was calculated to determine the predictive accuracy of fetal pulmonary artery doppler evaluation for neonatal respiratory distress.

APGAR 1min in fetuses without respiratory distress had a mean value of 8.05, and those who suffered from RDS had a mean APGAR score of 3.83. APGAR 5 min in fetuses without RDS had a mean value of 8.90, and those with RDS had a mean value of 3.80. Fetuses with RDS were admitted to neonatal intensive care. They were given oxygen, CPAP support or mechanical ventilation per individual requirement.

There was a significant difference in the main pulmonary artery (MPA) AT/ET ratio among fetuses which developed neonatal respiratory distress versus those which did not. We found that AT/ET the ratio was lower in fetuses which developed neonatal respiratory distress (0.24 ± 0.06 versus 0.34±0.03, P value = 0.001). The MPA PI values were high in fetuses developing respiratory distress (2.29 ± 0.21 versus 2.02 ± 0.27). A similar trend was observed with RI values (0.87±0.07/cm/s versus 0.79±0.08 cm/s) with P value of 0.003 and 0.003, respectively. The mean PSV was 77.69 cm/sec for fetuses who developed respiratory distress and 79.95 cm/sec for those who did not, with a p-value of 0.538, indicating no statistically significant link between PSV and the development of respiratory distress syndrome. The S/D ratio also did not differ considerably between the two groups. [Table-1]
The sensitivity and specificity of AT/ET ratio for predicting the development of RDS were higher than that for PI and RI values. For a cutoff value of 0.30 for AT/ET ratio, the receiver operating characteristic curve analysis revealed a sensitivity and specificity of 98.3% and 86.6%, respectively, for the risk of developing neonatal respiratory distress with an area under the curve of 0.912. [Table-2] [Figure-2]

Discussion

An evaluation of fetal main pulmonary artery doppler parameters was performed in this study to determine the efficacy of these markers in predicting newborn respiratory distress syndrome (RDS) development in late preterm pregnancies (newborns born between 34 and 36 weeks 6 days of pregnancy).

The findings of our study revealed that fetuses who developed RDS had considerably lower AT/ET and higher PI and RI compared to fetuses that did not develop RDS. Fetuses with RDS experience decreased pulmonary blood flow and increased pulmonary vascular resistance as compared to the healthy ones. Few previous studies have shown that MPA AT/ET was lower in preterm fetuses with RDS, which concurs with our findings.

Schenone et al. found a positive correlation between main pulmonary artery AT/ET ratio and surfactant/albumin ratio (measured in the amniotic fluid), suggesting that high AT/ET values predicted better lung maturity and thus lower risk of neonatal respiratory RDS [6]. MPA AT/ET ratio in fetuses diagnosed with RDS is much lower than in those without (0.209 versus 0.332, P - 0.001), according to Moety and colleagues. With a sensitivity of 76.4 percent and a specificity of 91.6 percent observed that a cutoff value of 0.305 for AT/ET could predict the occurrence of newborn RDS in babies delivered between 34 and 38+6 weeks of gestation[7]. A study by Guan et al. found that in preterm fetuses, AT/ET ratio may predict the development of neonatal respiratory distress with a sensitivity and specificity of 71.4% and 93.1%, respectively. According to them, less than fifth percentile values of AT and AT/ET ratios for gestational age may predict fetuses at risk of developing neonatal RDS [8].

Khanipouyani et al. 2016 evaluated 145 patients to find whether main pulmonary artery Doppler indices correlate with fetal lung maturity. They found that AT/ET ratio shows solid predictive value. Furthermore, they concluded that a cut-off value of ≥0.34 was useful to determine lung maturity in fetuses of gestational age 28-37wks [9].

Azpurua et al., in 2010, found that AT/ET was inversely related to the lecithin/sphingomyelin ratio acquired by amniocentesis. However, due to the small sample size, they were unable to predict a definitive link between AT/ET and the development of clinical RDS [10].

Kim et al. in 2013 observed an inverse relationship between AT/ET ratio and lung maturity, which does not concur with the other studies. However, they had a relatively small sample size (37 mothers) which may have led to such results [11].

In our study, we observed that a cut-off value of 0.30 for AT/ET ratio in the fetal main pulmonary artery in late preterms (delivered between 34 and 36+6 weeks) was statistically significant in predicting the development of respiratory distress. This cut-off value (0.30) had a sensitivity and specificity of 98.3% and 86.67%, respectively, with an area under the curve (ROC) of 0.912. The Pulsatility Index and Resistive Index values also correlated with the risk of development of RDS, but they demonstrated poor sensitivity and specificity.

Figure 1 Doppler evaluation of Fetal Main Pulmonary Artery.
Fig1a.- Doppler evaluation of Fetal Main pulmonary artery. Fig 1b. - Acceleration time (AT) -40ms. Fig 1c.- Ejection time (ET) -220ms - Fetal pulmonary artery waveform pattern of 29 yr old female with a gestational age of 34w3 dys, with AT/ET ratio of 0.18. Baby delivered through normal vaginal delivery with APGAR 1min of 3.3. The baby had bradycardia, developed respiratory distress, and was on oxygen support for 3days.

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Table 1 Main pulmonary artery parameters of fetuses with and without neonatal respiratory distress syndrome

|                      | Fetuses without RDS | Fetuses with RDS | p-value |
|----------------------|---------------------|------------------|---------|
|                      | Mean    | SD     | Mean    | SD     |         |
| AUA (gestational age in weeks) | 35.84   | 1.21   | 36.02   | 1.54   | 0.634   |
| PSV (cm/sec)          | 79.95   | 12.46  | 77.69   | 0.62   | 0.538   |
| EDV (cm/sec)          | 11.63   | 3.53   | 9.88    | 2.92   | 0.082   |
| S/D                  | 8.09    | 1.55   | 8.19    | 0.17   | 0.865   |
| Pulsatility Index    | 2.02    | 0.27   | 2.29    | 0.21   | 0.003   |
| Resistive Index      | 0.79    | 0.08   | 0.67    | 0.07   | 0.003   |
| Acceleration Time (AT) in ms | 74.52  | 13.52  | 59.20   | 11.63  | 0.001   |
| Ejection Time (ET) in ms | 218.43 | 40.62  | 248.80  | 53.48  | 0.018   |
| AT/ET                | 0.34    | 0.03   | 0.24    | 0.06   | 0.001   |

Table 2 Analysis of the ROC curve and the area under the curve with sensitivity and specificity

| Test Result Variable(s) | Area under ROC curve | Std. Error | Asymptotic 95% Confidence Interval | p-value | Cut off | Sensitivity | Specificity |
|-------------------------|----------------------|------------|-----------------------------------|---------|---------|-------------|-------------|
|                         |                      |            | Lower Bound                       | Upper Bound |
| PI (cm/sec)             | 0.950                | 0.048      | 0.900                            | 1.000    | 0.003   | 2.18        | 93.30       | 70.00       |
| RI (cm/sec)             | 0.806                | 0.074      | 0.712                            | 0.898    | 0.003   | 0.86        | 80.00       | 71.67       |
| AT (ms)                 | 0.816                | 0.065      | 0.720                            | 0.913    | 0.001   | 58.00       | 93.33       | 60.00       |
| ET (ms)                 | 0.716                | 0.061      | 0.600                            | 0.836    | 0.010   | 214.00      | 93.30       | 53.30       |
| AT/ET                   | 0.912                | 0.059      | 0.901                            | 1.000    | 0.001   | 0.30        | 98.33       | 86.67       |

Figure 2 Receiver operator characteristic curve of AT/ET ratio with sensitivity on Y-axis and specificity on X-axis.

Our study only included cases which were delivered within 24 hours of ultrasound doppler evaluation. Thus, we cannot predict any change in the MPA doppler parameters across different times of gestation. More research is needed to establish if this applies to women who aren’t in labour or if there is any variation in these parameters with time. Also, a larger group of pregnant females should be evaluated over a more extended period of gestation (second and third trimester) to see if there can be early risk stratification for developing neonatal RDS.

Finally, using our findings, we may propose evaluating fetal MPA AT/ET as a noninvasive, reasonably accurate approach for risk stratification in late preterm pregnancies instead of going for invasive procedures. In addition, we propose that this measurement be routinely incorporated in all ultrasound examinations conducted in the late third trimester to improve patient care.

Because the risk of newborn respiratory distress syndrome is higher in fetuses with MPA AT/ET of less than 0.30, it is recommended that they be delivered to an institution with good neonatal care.

**Conclusion**

One of the most important and challenging decisions an obstetrician must make before delivering a preterm fetus is determining fetal lung maturity. Several studies have attempted to link fetal parameters and lung maturity. We discovered a statistically significant relationship between respiratory distress syndrome development in newborn fetuses and their main pulmonary artery doppler parameters, including PI, RI and AT/ET ratio. We found that a cutoff of 0.30 for the AT/ET ratio provides a statistically significant association with the development of neonatal respiratory distress with a sensitivity of 98.3%, and specificity of 86.6%. PI and RI demonstrated poorer sensitivity and specificity in predicting RDS development than AT/ET ratio. Our research found no statistically significant relationship with Peak systolic velocity, End diastolic velocity and S/D ratio.

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**Conflict of interest**

There are no conflicts of interest to declare by any of the authors of this study.
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