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Noninvasive Fetal Lung Maturity Prediction Based on Amniotic Fluid Turbidity Using Ultrasonic Histogram Measurement Function

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Abstract

Background: Amniotic fluid turbidity increases with fetal lung maturation due to vernix and lung surfactant micelles suspended in the amniotic fluid. This study focused on this phenomenon and evaluated the presence or absence of respiratory distress syndrome (RDS)/transient tachypnea of the newborn (TTN) by quantitatively assessing the brightness of the amniotic fluid turbidity using a noninvasive ultrasound histogram measurement function. **Methods:** We included cases of singleton pregnancies managed at the Niigata University Medical and Dental Hospital between November 2020 and March 2022. Histograms of amniotic fluid turbidity were measured at the center of the amniotic fluid depth, avoiding the fetus, placenta, and umbilical cord, with the gain setting set to 0, and the average value was obtained after three measurements. Histograms of fetal urine in the bladder were measured similarly. The value obtained by subtracting the fetal bladder brightness value from the amniotic brightness value based on histogram measurements was used as the final amniotic fluid brightness value. **Results:** We included 118 cases (16 of RDS/TTN and 102 of control). The gestational age of delivery weeks was correlated with amniotic fluid brightness (Spearman's rank correlation coefficient was 0.344; $p = 0.00014$). Amniotic fluid brightness values were significantly lower in the RDS/TTN group than in the control group (RDS/TTN: 16.2 ± 13.5, control: 26.3 ± 16.3; $p = 0.020$). The optimal cutoff value of amniotic fluid brightness to predict RDS/TTN was 20.3. For predicting RDS/TTN, the sensitivity, specificity, positive predictive value, and negative predictive value were 91.7%, 69.6%, 26.2%, and 94.1%, respectively. **Conclusions:** The quantitative value of the amniotic fluid brightness by histogram measurements may provide an easy and objective index for evaluating the presence or absence of RDS/TTN.

Keywords

Amniotic Fluid, Brightness, Fetal Lung, Histogram, Turbidity

1. Background

Traditionally, fetal lung maturity has been estimated using gestational age or by examining various components of the amniotic fluid, such as lecithin-sphingomyelin (L/S) ratio [1], surfactant/albumin ratio by fluorescence polarization [2] [3] [4], and lamellar body count [5] [6] [7] [8] [9]. However, the collection of amniotic fluid involves an invasive procedure called amniocentesis, and it is desirable to establish a noninvasive method for evaluating fetal lung maturity.

The amniotic fluid becomes turbid, and the brightness of the amniotic fluid increases with advancing gestational age, according to previous studies [10] [11]. After the third trimester of pregnancy, fetal sebaceous glands rapidly increase in activity, size, and number and secrete sebum, the main component of vernix. Vernix detaches from the fetal skin surface due to the interaction of the skin with pulmonary surfactant secreted by alveolar type II epithelial cells. The detached vernix and pulmonary surfactant form micelles and diffuse into the amniotic fluid, which is the main cause of increased amniotic turbidity [10] [11]. Brown *et al.* [12] found that amniotic fluid turbidity in the third trimester of pregnancy is most frequently caused by vernix and rarely due to meconium or hemorrhage.

In this study, we focused on the phenomenon of amniotic fluid turbidity due to the micelles of vernix and pulmonary lung surfactants. And the presence or absence of RDS/TTN was evaluated by quantitatively assessing the brightness of amniotic fluid turbidity using a noninvasive ultrasound histogram measurement function.

2. Methods

The cases included were 118 singleton pregnancies managed at the Niigata University Medical and Dental Hospital between November 2020 and March 2022. Amniotic fluid turbidity was measured within 24 h of delivery. All cases were measured between 30 weeks, 4 days, and 41 weeks, 4 days of gestation. The exclusion criteria were fetal malformations, antenatal steroid administration, clinical chorioamnionitis, oligohydramnios, neonatal asphyxia, meconium aspiration syndrome and the unavailability of data. The ultrasound examinations were performed by obstetrics-gynecology specialists using the Voluson E8 (GE Healthcare UK Ltd., Buckinghamshire, England) and a 4 - 10 Hz convex probe (RAB6-D; GE Healthcare UK Ltd., Buckinghamshire, England).

Histograms of amniotic fluid turbidity were measured at the center of the amniotic fluid depth, avoiding the fetus, placenta, and umbilical cord, with the gain

setting set to 0, with a region of interest (ROI) set at 1 × 1 cm. Subsequently, an average value was obtained after three measurements (**Figure 1(a)**). The brightness values from histogram measurements were not absolute because they were affected by the type of gel, amount of gel, pressure of the probe, the thickness of the maternal subcutaneous fat, and thickness of the uterine muscle layer, even if the frequency, depth, and gain were kept constant. Therefore, in this study, fetal urine in the bladder was selected as the control material, considering that the amniotic fluid is produced almost exclusively with fetal urine and is a serious component similar to amniotic fluid. Histograms of fetal urine were measured, avoiding any surrounding tissue, and the ROI was set to 0.5 × 0.5 to 1 × 1 cm, according to the size of the fetal bladder (**Figure 1(b)**). The value obtained by subtracting the fetal bladder brightness value from the amniotic fluid mean brightness value based on histogram measurements was set as the final amniotic fluid brightness value.

Maternal information including maternal age (in years) at delivery, percentage of nulliparity, body mass index (BMI), gestational age (GA) of delivery weeks, mode of delivery, and presence of complications (hypertensive disorders of pregnancy: HDP, gestational diabetes mellitus: GDM, and fetal growth restriction: FGR), and neonatal information, such as neonatal body weight and percentage of male infants, were extracted from the patient records. GA was determined by the date of embryo transfer in the case of in vitro fertilization or by fetal crown-rump length measured by ultrasonography at approximately 10 weeks gestation if the pregnancy was spontaneous. The estimated fetal weight (g) was calculated as 1.07 × biparietal diameter $(cm)^3$ + 0.30 × abdominal circumference $(cm)^2$ × femur length (cm), and FGR was defined as −1.5 standard deviations of the fetal measurement reference value in the Japanese Society of Ultrasound Medicine official announcement [13].

The diagnosis of respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN) was established by the neonatologist based on a combination of clinical symptoms, chest radiography findings, and clinical course. Chest radiographs for RDS showed diffuse reticulogranular shadows and bronchial

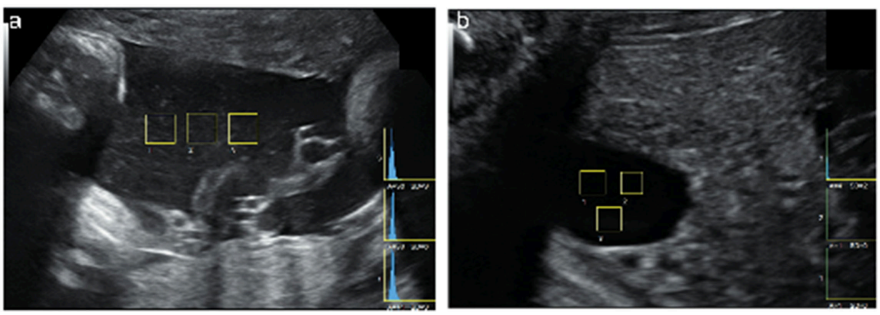

Figure 1. Histogram measurements of amniotic fluid and fetal bladder. Histogram measurements of amniotic fluid turbidity (a) and fetal bladder (b) from 1 × 1 cm region of interest in a fetal transverse B-mode image at 37 weeks 5 days gestation. The lower right graphs depict analyses of histogram results, where "A" represents the mean tone in the region of interest and "SD" represents the standard deviation.

translucency. Chest radiographic findings for TTN were enhanced hilar vasculature and bronchial translucency, a flat diaphragm, and the presence of fluid in the interlobar fissure or pleural space. The control group consisted of neonates without RDS or TTN.

Data were collected and entered into a spreadsheet (Excel; Microsoft, Tokyo, Japan) and statistically analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and GraphPad Prism 9 (v.9.0; GraphPad Software, Inc., La Jolla, CA, USA). Statistical methods included the Mann-Whitney U test, Fisher's exact test, Spearman's rank correlation coefficient, and receiver operating characteristic (ROC) curve, with $p < 0.05$ considered statistically significant.

This study was approved by the Institutional Ethical Review Board of Niigata University Graduate School (approval number 2020-0324). All examinees were given a detailed explanation before the procedure and written informed consent was obtained.

3. Results

We analyzed 118 cases (Table 1), and the mean maternal age was 35.4 ± 5.2 (range 23 - 48) years, 51 (43.2%) were nulliparous, the mean BMI was 25.5 ± 3.3 (range 19.3 - 35.5) kg/m^2, mean GA of delivery weeks was 37.2 ± 1.9 (range 30 - 41) weeks, and 18 (15.3%) were vaginal delivery. Mean neonatal body weight was 2755.8 ± 588.0 (range 960 - 3540) g, and 69 (58.5%) were male neonates. Five neonates (4.2%) were diagnosed with RDS, and 11 (9.3%) with TTN. Eight cases (6.8%) had HDP, ten (8.5%) had GDM, and nine (7.6%) had FGR. The correlation between GA at delivery weeks and amniotic fluid brightness is shown in Figure 2. Spearman's rank correlation coefficient was 0.344 ($p = 0.00014$).

Table 1. Patients' demographic data and the neonatal outcome.

Demographic data	
Maternal age (years)	35.4 (±5.2)
Nulliparity	51 (43.2%)
Body mass index (kg/m^2)	25.5 (±3.3)
GA at delivery (weeks)	37.2 (±1.9)
Vaginal delivery	18 (15.3%)
Neonatal body weight (g)	2755.8 (±588.0)
Male neonate	69 (58.5%)
RDS/TTN	16 (13.6%)
HDP	8 (6.8%)
GDM	10 (8.5%)
FGR	9 (7.6%)

Values are means (± standard deviation) or number of cases (%). GA, gestational age; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; FGR, fetal growth restriction, RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

The background and characteristics of the RDS/TTN and control groups are presented in Table 2. Maternal years of age at delivery, percentage of nulliparity, mode of delivery, and GDM were not significantly different between the two groups. The RDS/TTN group had significantly earlier GA of delivery weeks ($p = 0.00062$), significantly lighter birth weight ($p = 0.00029$), and significantly more maternal HDP ($p = 0.0011$) and FGR ($p = 0.019$) than the control group. Amniotic fluid brightness values were significantly lower in the RDS/TTN group compared to the control group (RDS/TTN group: 16.2 ± 13.5, control group: 26.3 ± 16.3; $p = 0.020$; Figure 3). The cutoff value of amniotic fluid brightness to predict RDS/TTN was analyzed using the ROC curve (Figure 4). The cutoff value of 20.3 (area under the ROC curve [AUC]: 0.707, 95% confidence interval [CI]: 0.568 - 0.846) had a sensitivity of 81.2%, a specificity of 67.6%, a positive predictive value of 27.7%, and a negative predictive value of 95.8%. Scattergrams for the amniotic fluid brightness in cases with RDS/TTN and in controls are shown in Figure 5.

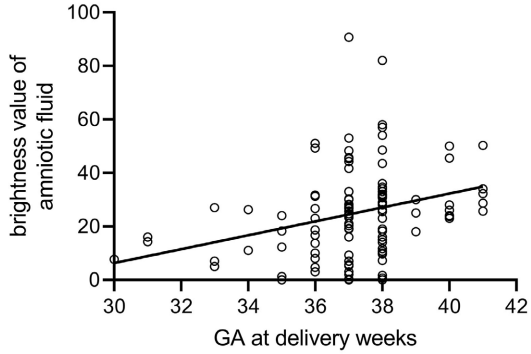

Figure 2. The correlation between GA at delivery weeks and amniotic fluid brightness. Spearman's rank correlation coefficient was 0.344 ($p = 0.00014$). GA, gestational age.

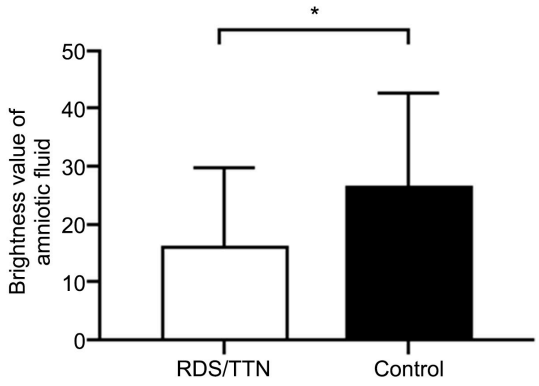

Figure 3. Comparison of amniotic fluid brightness values in the RDS/TTN and control groups. The amniotic fluid brightness value in the RDS/TTN group (16.2 ± 13.5) was significantly less than that in the control group (26.3 ± 16.3) ($p = 0.020$). Error bars indicate standard deviation. RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

Table 2. Background and characteristics of RDS/TTN cases compared with controls.

	RDS (n = 5)	TTN (n = 11)	RDS/TTN (n = 16)	Control (n = 102)	p-value
Maternal age (years)	35.8 (±7.2)	35.1 (±4.9)	35.3 (±5.7)	35.4 (±5.1)	0.933
Nulliparity	3 (60.0%)	1 (9.1%)	4 (25.0%)	47 (46.0%)	0.114
Body mass index (kg/m^2)	23.6 (±1.3)	26.2 (±3.4)	25.4 (±3.2)	25.5 (±3.3)	0.880
GA at delivery (weeks)	33.0 (±2.4)	35.6 (±2.0)	34.8 (±2.5)	37.5 (±1.5)	<0.001
Vaginal delivery	0 (0%)	2 (18.2%)	2 (12.5%)	16 (15.7%)	0.742
Neonatal body weight (g)	1552 (±415.6)	2329 (±574.1)	2086 (±640.5)	2861 (±504.3)	<0.001
Male neonate	2 (40.0%)	6 (54.5%)	8 (50.0%)	61 (59.8%)	0.640
HDP	3 (60.0%)	2 (18.2)	5 (31.3%)	3 (2.9%)	0.001
GDM	1 (20.0%)	0 (0%)	1 (6.3%)	9 (8.8%)	0.731
FGR	1 (20.0%)	3 (27.3%)	4 (25.0%)	5 (4.9%)	0.019

Values are means (±standard deviation) or number of cases (%). The control group consists of neonates having neither RDS nor TTN. RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn; GA, gestational age; HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; FGR, fetal growth restriction. p-values show the comparison of RDS/TTN and control groups.

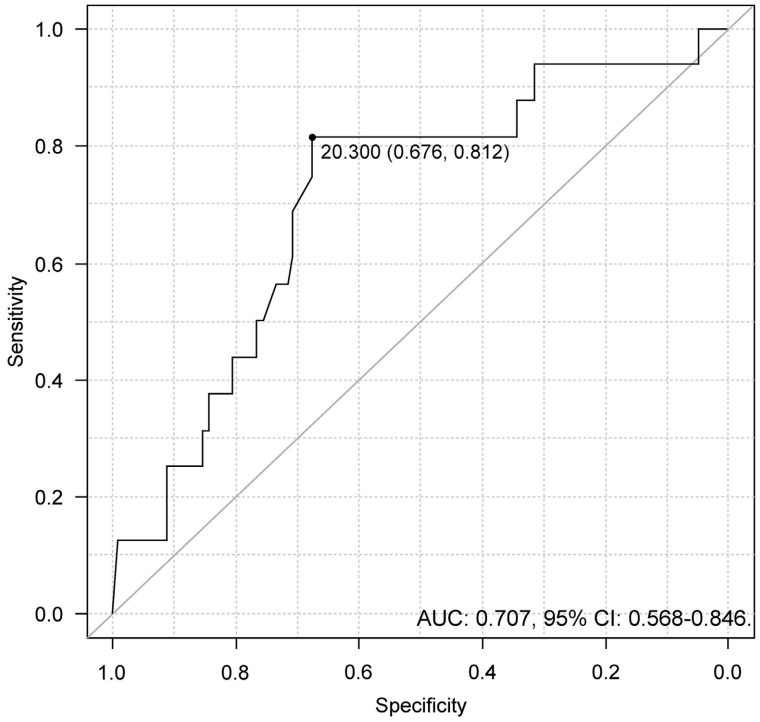

Figure 4. Receiver operating characteristic (ROC) curve of the studies on amniotic fluid brightness value in their capacity to predict neonatal respiratory disorders (respiratory distress syndrome/transient tachypnea of the newborn). The cutoff value of the amniotic fluid brightness value was 20.3. The area under the ROC curve was 70.7%, the 95% confidence interval (CI) was 0.568 - 0.846, the sensitivity was 81.2%, the specificity was 67.6%, the positive predictive value was 27.7%, and the negative predictive value was 95.8%.

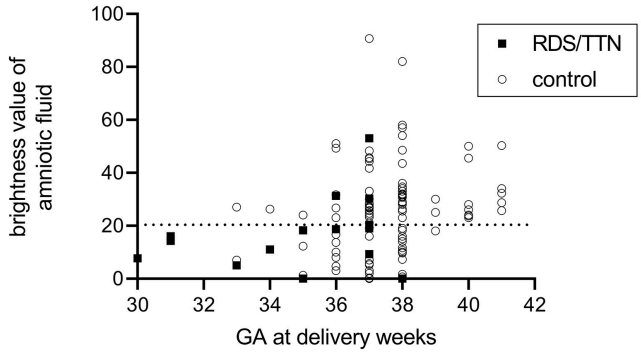

Figure 5. Scattergram showing the amniotic fluid brightness in the RDS/TTN neonates and controls. The dot-dash bar indicates the cutoff value for the occurrence of RDS/TTN in the present study. RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

4. Discussion

The present study showed that GA and amniotic fluid brightness were positively correlated. This is thought to reflect the phenomenon shown by Narendran [10] and Nishijima [11] that amniotic fluid turbidity increases with advancing gestational age due to the floating micelles of vernix and pulmonary surfactant in the amniotic fluid using the histogram measurement function as in this study. However, the measurement method needs to be further developed. In this study, measurements were performed at three locations in the center of the amniotic fluid depth for simplicity while avoiding the fetus, placenta, and umbilical cord, and the average value was used for analysis. Since the measurements were taken in the supine position, gravity might have caused gradations and arbitrary biases. It is necessary to consider a more reproducible measurement method in the future. In addition, molecular and biochemical approaches should be used to confirm whether the amniotic fluid brightness in the histogram measurement reflects the increase of vernix and pulmonary surfactant micelles. As a future research project, we would like to collect amniotic fluid samples and visually confirm the micelles of vernix and pulmonary surfactant using electron microscopy.

In this study, a high negative predictive value of 95.8% was obtained by setting the cutoff value of amniotic fluid brightness by ultrasonic histogram measurement to 20.3 as an indicator of the presence or absence of RDS/TTN. In other words, an increase in the amniotic fluid brightness value above 20.3 suggested a high probability of neonates with absence of RDS/TTN. This study used a noninvasive method of evaluating fetal lung maturation using ultrasonography that anyone can measure with a normal B-mode image. Moreover, the amniotic fluid brightness was evaluated as quantitative values using a histogram measurement function. The noninvasive ultrasonography technique can avoid complications of amniocentesis (such as miscarriage and fetal death, premature membrane rupture, and chorioamnionitis).

For several decades, several approaches have been attempted to non-invasively

estimate fetal lung maturation, including direct grayscale measurement of the fetal lung [14] [15], fetal lung tissue movement [16] [17], and the relationship between lung tissue and liver tissue [18]. Recently, a texture analysis method [19] was devised to quantify changes in fetal lung tissue and applied to predict fetal lung maturation. Several reports have correlated amniotic fluid brightness with fetal lung maturation. Cetrulo *et al.* [20] correlated amniotic fluid brightness measured at 650 nm optical density with pulmonary surfactants in the amniotic fluid. Moreover, a report correlated newspaper-unreadable turbid amniotic fluid with L/S ratio and phosphatidylglycerol to assess lung maturation [21], and findings, such as snowstorms and blizzards, in amniotic fluid can assess fetal lung maturation [22]. However, the ultrasonographic findings in the amniotic fluid reported thus far are not quantified indicators, as shown in this study.

This study had some limitations. First, there were few cases in the preterm period, which resulted in a difference in the GA at delivery weeks in the background of the RDS/TTN and control groups. The GA at delivery weeks is an important factor in evaluating fetal maturation. Based on the results of this study, we need to conduct a multicenter study and analyze a larger number of cases in the future. Second, the number of vaginal delivery cases was small; hence, we could not analyze differences in delivery mode. The cases of the scheduled cesarean section have many opportunities for ultrasound evaluation within 24 h of delivery because the patient is hospitalized from the day before surgery, whereas it is difficult to evaluate ultrasound within 24 h of delivery in vaginal deliveries. There are several reports that cesarean section is associated with a higher risk of TTN than vaginal delivery [23] [24] [25], and further case accumulation is desirable to include differences in delivery modes. Third, we could not analyze cases of antenatal steroid administration, although new findings may be obtained if changes in amniotic fluid brightness due to antenatal steroid administration can be observed.

5. Conclusion

A high negative predictive value of 95.8% was obtained using a cutoff value of 20.3 for the amniotic fluid brightness value by histogram measurement as an indicator of the presence or absence of RDS/TTN. The quantitative value of the amniotic fluid brightness by histogram measurement may provide an easy and objective index for evaluating the presence or absence of RDS/TTN.

Ethics Approval and Consent to Participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Institutional Ethical Review Board of Niigata University Graduate School (approval number 2020-0324). Written informed consent was obtained from all patients included in this study.

Authors' Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Kensuke Matsumoto, Kaoru Yamawaki, and Kazufumi Haino. Kaoru Yamawaki and Kazufumi Haino contributed to investigation, resources, and supervision. Kaoru Yamawaki, Kazufumi Haino, and Koji Nishijima contributed to writing, reviewing, and editing. The first draft of the manuscript was written by Kensuke Matsumoto, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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