Fetal Diagnosis and Therapy

Original Paper

Fetal Diagn Ther 2020;47:636–641
DOI: 10.1159/000507550

Received: June 16, 2019
Accepted: March 25, 2020
Published online: July 10, 2020

Assessment of Fetal Lung Maturity Using Quantitative Ultrasound Analysis in Patients with Prelabor Rupture of Membranes

Fernanda Borges Flosi[a] Fernanda Campos da Silva[b]
Guilherme Ramires de Jesús[c, d] Luis Guillermo Coca Velarde[e]
Renato Augusto Moreira de Sá[a, d]

[a]Medical Sciences Post Graduation, Universidade Federal Fluminense, Niterói, Brazil; [b]Department of Obstetrics, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; [c]Department of Obstertics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; [d]Department of Obstetrics, Instituto Fernandes Figueira – FIOCRUZ, Rio de Janeiro, Brazil; [e]Department of Statistics, Universidade Federal Fluminense, Niterói, Brazil

Keywords
Premature rupture of membrane · Fetal lung maturity · Neonatal respiratory morbidity · Respiratory distress syndrome · Newborn · Quantitative ultrasound analysis

Abstract
Introduction: Prelabor rupture of membranes (PROM) is a frequent clinical situation, and the decision about the best time for delivery remains controversial, mainly due to the risk of neonatal respiratory morbidity (NRM). Assessment of fetal lung maturity using ultrasound, a safe method and widely used in current obstetrical practice, could change this scenario. This study was designed to evaluate the ability of quantitative ultrasound method QuantusFLM® to predict NRM in patients with PROM and whether maternal BMI, gestational age, occurrence of the disease, and presence of oligohydramnios influenced the performance. ***Methods:*** Patients with singleton gestations, diagnosis of PROM, and gestational age between 24 and 38 weeks and 6 days were included. Fetal lung image was acquired by ultrasound within 48 h prior to delivery and analyzed by QuantusFLM®. The results were then paired with neonatal outcomes to assess the program's ability to predict the NRM in this specific group. A logistic regression model was created to analyze factors that could affect the test results. ***Results:*** Fifty-four patients were included. Mean maternal BMI was 28.99 kg/m^2, and in 25 patients (46.2%), oligohydramnios was observed at the time of examination. Mean gestational age at delivery was 35 weeks and 4 days, and the NRM prevalence was of 18.5%. QuantusFLM® predicted NRM with a 60% sensitivity, 79.5% specificity, 40% positive predictive value, 89.7% negative predictive value, and 75.6% accuracy. Maternal BMI, disease occurrence, presence of oligohydramnios, and gestational age did not interfere with the evaluation. ***Conclusion:*** This study demonstrates a good accuracy of QuantusFLM® as a NRM predictor in patients with PROM, with particular reliability in identifying that pulmonary maturity has already occurred.

karger@karger.com
www.karger.com/fdt

Renato Augusto Moreira de Sá
Universidade Federal Fluminense, Centro de Ciências Médicas
Hospital Universitário Antônio Pedro
Av. Marquês do Paraná, 303, Niterói 24033900 (Brazil)
renatosa.uff@gmail.com

Introduction

Prelabor rupture of membranes (PROM) affects 8% of full-term pregnancies and 2% of pregnancies <37 weeks, being associated with 40% of preterm births [1]. In the absence of maternal or fetal indications for immediate delivery, management is currently based on gestational age. Delivery is recommended after 34 weeks of pregnancy, while expectant management should be considered before that gestational age [1, 2].

However, this ideal gestational age for delivery remains controversial due to the risk of respiratory complications, which remains high for newborns classified as late preterm (between 34 and 36 weeks and 6 days) or as early term (between 37 and 38 weeks and 6 days). In this context, a test to assess the risk of neonatal respiratory morbidity (NRM) may be a helpful tool to decide the best time of delivery.

The most widely used methods for assessing fetal lung maturity in current clinical practice relies on an amniocentesis and fluid analysis, with risks of placental abruption, maternal and/or fetal hemorrhage, infection, and anticipation of delivery [3]. Recently, a quantitative ultrasonographic method for evaluating the risk of NRM was developed (QuantusFLM®), with similar accuracy to that found in biochemical tests performed on the amniotic fluid [4, 5].

This test was previously validated in a multicenter study [5], but there was no specific analysis of patients with PROM. Oligohydramnios is often present in this context, acting as a limiting factor for the accomplishment of an obstetric ultrasonographic study [6] and could interfere with the results of the test. Therefore, this study was designed to evaluate the performance of QuantusFLM® in predicting NRM in a series of patients with PROM.

Materials and Methods

This was a prospective observational study in 2 maternities in Rio de Janeiro, Brazil (Clínica Perinatal de Laranjeiras and Hospital Universitário Antônio Pedro), performed from June 2016 until December 2018. Patients with singleton pregnancies, without previous diagnosis of congenital and/or genetic anomalies and with diagnosis of PROM between 24 and 38 weeks and 6 days were invited to participate in the study. Only patients whose delivery occurred up to 48 h after ultrasound evaluation were included, to ensure that QuantusFLM® result was related to the neonatal result. All patients have given their written informed consent, and the study protocol was approved by both institutes' committees on human research. Exclusion criteria applied were administration of corticosteroids for fetal lung maturation after ultrasound evaluation, sonographic evaluation of fetal lung with poor quality for evaluation by QuantusFLM® program, decline to participate or to sign the consent form, and neonatal sepsis, as this diagnosis could increase the incidence of NRM regardless of the stage of lung maturity.

Ultrasound examination was performed in all eligible patients by the principal investigator of the study (FBF) using General Electric Healthcare machines (Pollards Wood, UK) previously validated by QuantusFLM®, using an abdominal probe with 2–6 MHz of frequency. An axial image of fetal thorax was obtained as recommended by the manufacturers, at the level of 4 chamber heart view and without any postprocessing manipulation. The thorax occupied two-thirds of the screen, and there were no significant shadows in fetal lungs deriving from ribs or spine. The image was saved as DICOM file and sent to the commercial Web site of QuantusFLM® (www.quantusflm.com) [4, 7].

After submission, the result was available in the online platform up to 120 min, being expressed as "high risk" or "low risk" of NRM. The PI, the assistant obstetrician, and the neonatologists were blinded for this analysis, to avoid interference of the result in obstetric management. The decision of the moment for delivery was made by the assistant obstetrician, using current protocols for PROM [1, 2]. Neonatal care was also performed by the assistant pediatric team, without any influence of the investigators. During ultrasound examination for acquisition of lung images, amniotic fluid was evaluated measuring the deepest vertical pocket, considering oligohydramnios when the deepest vertical pocket was below 2 cm and polyhydramnios when above 8 cm [8].

Data about delivery and neonatal outcomes were retrieved reviewing medical charts, and a descriptive statistical analysis was performed. The main outcome was occurrence of NRM, which includes transient tachypnea of the newborn (TTN) and respiratory distress syndrome (RDS). Secondary outcomes were the 5-min Apgar score, neonatal resuscitation in the delivery room, admission to neonatal intensive care unit, length of stay in neonatal intensive care unit, and neonatal death.

TTN was defined as (1) respiratory distress (tachypnea, nasal flaring, chest retraction, or need for oxygen to prevent hypoxemia of <40%), with a benign and self-limiting course, beginning in the first 30 min of life, persisting for at least 6 h, and resolution in up to 96 h; (2) chest X-ray evidencing fluid retention; and (3) absence of any concurrent diagnosis to explain respiratory distress [9]. The definition of RDS was (1) evidence of respiratory distress (tachypnea, chest retractions, or nasal flaring) immediately after delivery and requiring respiratory support (oxygen or ventilation with positive pressure) for at least 24 h, (2) administration of exogenous pulmonary surfactant, and/or (3) a chest X-ray with hyaline membrane disease [3].

Performance of QuantusFLM® to predict NRM in patients with PROM was calculated in a 2×2 contingency table, using data about risk analysis and neonatal outcome, and one proportion test was used to compare the accuracy of the current study with previously published validation study [5]. The Kappa (κ) coefficient was also calculated to express the reliability of the test.

To evaluate if oligohydramnios, maternal BMI, route of delivery, and the own occurrence of the NRM would influence the test results, a logistic regression model was created considering if the reported risk was compatible with the neonatal outcome. First, the variables were tested separately and then included in the model one by one.

Results

The study included 54 patients with PROM, and there were no losses according to the exclusion criteria. Five patients with PROM and expectant management were eligible for the study but were not included because of rapid evolution to labor, precluding the acquisition of ultrasonographic fetal lung image.

Demographic and pregnancy-related characteristics are described in Table 1. Mean gestational age of the PROM diagnosis was 34 weeks and 4 days, and in 25 patients (46.3%), oligohydramnios was observed at the time of the examination.

Results of delivery and neonatal outcomes are shown in Table 2. Mean gestational age at delivery was 35 weeks and 5 days and mean interval between the diagnosis of PROM and childbirth was 5.3 days. Eleven patients had delivery before 34 weeks and in 43 patients delivery occurred with 34 weeks or more. Only 6 patients (11.1%) underwent vaginal delivery, while 3 patients (5.6%) had intrapartum cesarean section and 45 patients (83.3%) were submitted to cesarean section without labor.

Ten newborns developed respiratory morbidity (18.5%), 9 of whom had newborn RDS (16.7%) and one had a TTN (1.8%). The rate of NRM in late preterm infants was 13.1% (3/23), while there was no respiratory morbidity in early-term infants (0/20). There were no neonatal deaths.

Table 3 describes the performance of QuantusFLM® in this study: considering all included patients, sensitivity was 60%, specificity was 79.5%, and positive likelihood ratio was 2.93, with a negative likelihood ratio of 0.50. Positive predictive value was of 40%, while negative predictive value was of 89.7% and the test accuracy was 75.9%. Kappa coefficient was 0.33, suggesting a fair agreement between the test result and the absence or presence of the disease.

Logistic regression assessed the relationship between test accuracy and the presence of disease (NRM), maternal BMI, presence of oligohydramnios, and gestational age at ultrasound evaluation, as shown in Table 4. The results suggest that none of the variables influenced the accuracy of the test.

Using one proportion test, we compared the accuracy of our study (75.9%) with previously published results (86%) [5]. With a null hypothesis of 0.86, there was no statistical difference between the 2 studies (Z statistic 0.0796, 95% CI 0.00017–8.0347%; $p = 0.93$). Delivery route was not analyzed as an independent variable for the outcome considering the high cesarean rates in this study.

Table 1. Maternal demographics and pregnancy-related characteristics

	Total (n = 54)
Maternal age, years	32.52 (25–45)
Nulliparity	33 (61.1%)
Comorbidities	20 (37%)
Maternal BMI, kg/m^2	28.99 (22.1–37.5)
Gestational age at the time of diagnosis of PROM, weeks (min.–max.)	34.5 (22.7–38.7)
Corticosteroid therapy	21 (38.8%)
Corticosteroid-to-delivery interval, days	9.7 (0–39)
Oligohydramnios	25 (46.3%)

Data expressed as mean (variation) or n (%), when appropriate. PROM, prelabor rupture of membranes.

Table 2. Delivery and neonatal outcomes

	Total (n = 54)
Gestational age at birth, weeks	35.5 (25.1–38.7)
Interval between PROM and birth, days	5.3 (0–76)
Type of birth	
Vaginal delivery	6 (11.1%)
Cesarean section without labor	45 (83.3%)
Cesarean section in labor	3 (5.6%)
Female newborn	28 (51.8%)
Birth weight, g	2,376 (795–3,435)
Apgar <7 in the 5th min	1 (1.8%)
Resuscitation in delivery room	5 (9.2%)
Admission to NICU	20 (37.0%)
Length of stay in NICU, days	30.88 (4–133)
NRM	10 (18.5%)
Respiratory distress syndrome	9 (16.6%)
TTN	1 (1.8%)
Neonatal death	0

Data expressed as mean (variation) or n (%), when appropriate. NICU, neonatal intensive care unit; PROM, prelabor rupture of membranes; NRM, neonatal respiratory morbidity; TTN, transient tachypnea of the newborn.

Discussion/Conclusion

The present study demonstrated that evaluation of the risk of NRM through quantitative analysis of fetal lung texture by QuantusFLM® had good accuracy (75.9%) in patients with PROM whose delivery occurred between 24 and 38 weeks and 6 days. Negative predictive value of the test can be considered the most relevant feature (89.7%), indicating that the test is especially reliable in affirming that pulmonary maturity has already occurred.

Table 3. Performance of QuantusFLM® in prediction of NRM in patients with PROM

	Total number of patients (n = 54)	Delivery with <34 weeks (n = 11)	Delivery with ≥34 weeks (n = 43)
Sensitivity	60.0% (6/10)	71.4% (5/7)	33.3% (1/3)
Specificity	79.5% (35/44)	75.0% (3/4)	80.0% (32/40)
Positive likelihood ratio	2.93	2.85	1.66
Negative likelihood ratio	0.50	0.38	0.83
Positive predictive value	40.0% (6/15)	83.3% (5/6)	11.1% (1/9)
Negative predictive value	89.7% (35/39)	60.0% (3/5)	94.1% (32/34)
Accuracy	75.9% (41/54)	72% (8/11)	76.7% (33/43)

PROM, prelabor rupture of membranes; NRM, neonatal respiratory morbidity.

Table 4. Logistic regression evaluating the relationship between test accuracy and selected variables

Variables	OR (95% CI)
Oligohydramnios	0.89 (0.29–2.65)
Gestational age at ultrasound evaluation	1.23 (0.99–1.52)
Maternal BMI	0.97 (0.84–1.12)
NRM	0.35 (0.08–1.58)

NRM, neonatal respiratory morbidity.

The results are similar to those reported by other tests for evaluation of fetal lung maturity [4, 5]. However, the most accurate tests are performed on amniotic fluid obtained through amniocentesis – an invasive procedure with risks to maternal-fetal binomial. For this reason, they have low acceptance by patients and are often underutilized [5]. One advantage of QuantusFLM® is to use ultrasonography, a noninvasive, safe, and widely performed exam in today's obstetrical practice [10]. In addition, quantitative analysis of the fetal lung texture allows a computerized evaluation of the image, removing subjective feature of the method [4].

Another positive aspect of the test is the knowledge of fetal lung maturity through the remote analysis of an ultrasound image (via online platform of the program). This favors the applicability of QuantusFLM® in most centers, since ultrasound is widely available and easily performed, contrasting to tests performed on the amniotic fluid which require shipping of the biologic material to a specialized laboratory for analysis [11]. In this context, it can even be used in regions with low medical resources when maternal transfer to more qualified centers is considered [12].

QuantusFLM® was previously evaluated in a large, prospective multicenter study published by Palacio et al. [5]. These authors analyzed 730 patients between 25 and 38 weeks and 6 days, with a prevalence of NRM of 13.8%. QuantusFLM® was able to predict this event with 74.3% sensitivity, 88.6% specificity, and a positive predictive value of 51% and negative predictive value of 95.5%. The reported accuracy was 86.5% for prediction of NRM through this method, with no statistical difference to the accuracy found in this study [5].

Although the publication of Palacio et al. included patients diagnosed with PROM, the authors did not evaluate the performance of QuantusFLM® in this subgroup separately. Due to controversy about the best time for delivery [2], as well as possibility of technical difficulty to perform ultrasonographic examination in these patients [6], we consider the evaluation of performance of QuantusFLM® in this specific subgroup of patients to be particularly relevant. According to literature review, this is the first study to evaluate the performance of QuantusFLM® exclusively in patients with PROM, evaluating whether amniotic fluid volume and maternal BMI could interfere with the performance of the test.

The incidence of NRM found in the present study was of 18.5%, similar to that found in other publications [5]. When the group of late preterm infants was analyzed, the observed rate of NRM was 13.1%. It should be emphasized that current guidelines recommend prompt delivery after 34 weeks in patients with PROM, without administration of corticosteroids or evaluation of fetal lung maturity [1, 2].

Considering the high rates of NRM described above, the use of QuantusFLM® analysis could individualize the administration of corticosteroid in patients diagnosed with PROM and gestational age between 34 and 36 weeks

and 6 days. This could contribute to reduce neonatal morbidity, as already verified with use of corticosteroid therapy at this gestational age in patients with PROM as well as intact membranes [13].

The recommendation of immediate delivery – proposed in current guidelines [1, 2] – is based on the fact that disability-free survival after late preterm birth is high [14]. However, there is a growing concern about the risks of adverse outcomes of this group, with reports of increased risk of neonatal morbidity [15], hospital admission in early childhood [16], and academic limitations in school-age children compared to term newborns [17].

The present study also had as objective the evaluation of some factors that could interfere in the accuracy of the test. Oligohydramnios complicates 37–45% of cases of preterm PROM [18] and may be a limiting factor for performing obstetric ultrasound in these patients since it worsens the accuracy of the examination [6]. However, the current study did not demonstrate a statistical difference in the ability to predict the risk of NRM by QuantusFLM® in patients with oligohydramnios compared to patients who presented with normohydramnios or polyhydramnios at the time of examination.

Regarding maternal BMI, it is known that adipose tissue promotes attenuation of sound beams, with consequent decrease in the quality of the ultrasound image [19]. Similarly to the volume of amniotic fluid, however, maternal BMI also did not influence the accuracy of the test.

Despite being one of the objectives of the study, it was not possible to analyze the influence of route of delivery considering the high cesarean rate that occurred in this study. This is probably due in part to the design of the study, in which sonographic analysis of the fetal lung should occur within 48 h of delivery, favoring the recruitment of patients scheduled for cesarean section, as well as the high cesarean rates in Brazil, especially in private hospitals [20].

All ultrasonographic examinations in this study were performed by the same professional, post-graduated in fetal medicine, which probably justified the absence of loss of patients due to poor image quality compared to 15.6% of loss for this reason in the study published by Palacio et al. [5]. However, the acquisition of the fetal image for lung maturity analysis is technically simple and can be easily learned by a qualified professional, which favors the reproduction of these results.

This study has some limitations that need to be recognized. First, the number of included patients (54) was lower than other previous studies that evaluated the accuracy of QuantusFLM® [4, 5], especially when a subanalysis regarding gestational age at delivery was performed. Also, the analysis of factors that could influence the test accuracy should be interpreted with caution, as there were a small number of primary outcomes. Nonetheless, included patients belong to a specific subgroup diagnosed with PROM, a frequent and relevant complication in current obstetric practice [2]. In addition, the study was performed in only 2 centers and ultrasonographic images were obtained by a single professional, which may limit the generalization of the findings.

In conclusion, quantitative ultrasound method QuantusFLM® presented a good accuracy in prediction of NRM in patients with singleton gestations and PROM between 24 and 38 weeks and 6 days. The test shows particular reliability in identifying that pulmonary maturity has already occurred and may support the decision of delivery when the analysis reports a low risk of NRM, despite its small overall positive predictive value. This study also suggests that maternal BMI, presence of oligohydramnios, gestational age, and occurrence of the disease did not influence the predictive capacity of NRM by QuantusFLM®, although these results should be confirmed in larger studies.

Statement of Ethics

All patients gave their written informed consent, and the study protocol was approved by the institute's committee on human research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no external funding for this study.

Author Contributions

F.B.F. and R.A.L.: data acquisition, study design, writing, literature review, and statistical analysis. F.C.d.S. and G.R.d.J.: writing, literature review, and statistical analysis. L.S.C.V.: statistical analysis.

References

1 Royal College of Obstetricians & Gynaecologists. Preterm prelabour rupture of membranes green–top Guideline No. 44, November 2006. Minor Amendment October 2010.
2 Bulletins-Obstetrics CoP. ACOG practice bulletin no. 188: prelabor rupture of membranes. Obstet Gynecol. 2018;131(1):e1–14.
3 Azpurua H, Norwitz ER, Campbell KH, Funai EF, Pettker CM, Kleine M, et al. Acceleration/ejection time ratio in the fetal pulmonary artery predicts fetal lung maturity. Am J Obstet Gynecol. 2010;203(1):40–8.
4 Bonet-Carne E, Palacio M, Cobo T, Perez-Moreno A, Lopez M, Piraquive JP, et al. Quantitative ultrasound texture analysis of fetal lungs to predict neonatal respiratory morbidity. Ultrasound Obstet Gynecol. 2015;45(4):427–33.
5 Palacio M, Bonet-Carne E, Cobo T, Perez-Moreno A, Sabrià J, Richter J, et al. Prediction of neonatal respiratory morbidity by quantitative ultrasound lung texture analysis: a multicenter study. Am J Obstet Gynecol. 2017;217(2):196.e1–e14.
6 Barnhard Y, Bar-Hava I, Divon MY. Accuracy of intrapartum estimates of fetal weight. Effect of oligohydramnios. J Reprod Med. 1996;41(12):907–10.
7 Burgos-Artizzu XP, Perez-Moreno Á, Coronado-Gutierrez D, Gratacos E, Palacio M. Evaluation of an improved tool for non-invasive prediction of neonatal respiratory morbidity based on fully automated fetal lung ultrasound analysis. Sci Rep. 2019;9(1):1950.
8 Moise KJ. Toward consistent terminology: assessment and reporting of amniotic fluid volume. Semin Perinatol. 2013;37(5):370–4.
9 Weintraub AS, Cadet CT, Perez R, DeLorenzo E, Holzman IR, Stroustrup A. Antibiotic use in newborns with transient tachypnea of the newborn. Neonatology. 2013;103(3):235–40.
10 Fowlkes JB; Bioeffects Committee of the American Institute of Ultrasound in Medicine. American Institute of Ultrasound in Medicine consensus report on potential bioeffects of diagnostic ultrasound: executive summary. J Ultrasound Med. 2008;27(4):503–15.
11 Grenache DG, Gronowski AM. Fetal lung maturity. Clin Biochem. 2006;39(1):1–10.
12 Damron DP. Fetal lung maturity testing. Am J Obstet Gynecol. 2014;211(2):184–5.
13 Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14):1311–20.
14 Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, et al. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet. 2016;387(10017):444–52.
15 Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics. 2006;118(3):1207–14.
16 Lain SJ, Nassar N, Bowen JR, Roberts CL. Risk factors and costs of hospital admissions in first year of life: a population-based study. J Pediatr. 2013;163(4):1014–9.
17 McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: a systematic review. Pediatrics. 2011;127(6):1111–24.
18 Ekin A, Gezer C, Taner CE, Ozeren M. Perinatal outcomes in pregnancies with oligohydramnios after preterm premature rupture of membranes. J Matern Fetal Neonatal Med. 2015;28(16):1918–22.
19 Tsai PJ, Loichinger M, Zalud I. Obesity and the challenges of ultrasound fetal abnormality diagnosis. Best Pract Res Clin Obstet Gynaecol. 2015 Apr;29(3):320–7.
20 Ramires de Jesus G, Ramires de Jesus N, Peixoto-Filho FM, Lobato G. Caesarean rates in Brazil: what is involved? BJOG. 2015;122(5):606–9.