OBSTETRICS

Prediction of neonatal respiratory morbidity by quantitative ultrasound lung texture analysis: a multicenter study

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BACKGROUND: Prediction of neonatal respiratory morbidity may be useful to plan delivery in complicated pregnancies. The limited predictive performance of the current diagnostic tests together with the risks of an invasive procedure restricts the use of fetal lung maturity assessment.

OBJECTIVE: The objective of the study was to evaluate the performance of quantitative ultrasound texture analysis of the fetal lung (quantusFLM) to predict neonatal respiratory morbidity in preterm and early-term (<39.0 weeks) deliveries.

STUDY DESIGN: This was a prospective multicenter study conducted in 20 centers worldwide. Fetal lung ultrasound images were obtained at 25.0–38.6 weeks of gestation within 48 hours of delivery, stored in Digital Imaging and Communication in Medicine format, and analyzed with quantusFLM. Physicians were blinded to the analysis. At delivery, perinatal outcomes and the occurrence of neonatal respiratory morbidity, defined as either respiratory distress syndrome or transient tachypnea of the newborn, were registered. The performance of the ultrasound texture analysis test to predict neonatal respiratory morbidity was evaluated.

RESULTS: A total of 883 images were collected, but 17.3% were discarded because of poor image quality or exclusion criteria, leaving 730 observations for the final analysis. The prevalence of neonatal respiratory morbidity was 13.8% (101 of 730). The quantusFLM predicted neonatal respiratory morbidity with a sensitivity, specificity, positive and negative predictive values of 74.3% (75 of 101), 88.6% (557 of 629), 51.0% (75 of 147), and 95.5% (557 of 583), respectively. Accuracy was 86.5% (632 of 730) and positive and negative likelihood ratios were 6.5 and 0.3, respectively.

CONCLUSION: The quantusFLM predicted neonatal respiratory morbidity with an accuracy similar to that previously reported for other tests with the advantage of being a noninvasive technique.

Key words: amniocentesis, amniotic fluid analysis, biomarker, computational methods, diagnostic indices, fetal lung maturity, neonatal respiratory morbidity, predictive values, quantitative texture analysis, respiratory distress syndrome, sonography, transient tachypnea, ultrasound

Neonatal respiratory morbidity (NRM) due to of either respiratory distress syndrome or transient tachypnea of the newborn is the most common complication in infants born preterm and even early term (<39 weeks).[1-3] Assessment of fetal lung maturity for the prediction of NRM may be relevant, particularly after 34 weeks of gestation, when the risk of NRM ranges from 5% to 20%, to better assess the risk/benefit ratio of elective delivery in late pregnancy complications[4-6] and/or with the use of corticoisteroids.[7,8]

In current clinical practice, the evaluation of the risk of NRM relies on the study of different components of the amniotic fluid which requires an amniocentesis.[9,10]

Prediction of fetal lung maturity using fetal ultrasound has long been proposed as a noninvasive alternative to amniocentesis.[11,12] Several approaches using computer analysis of fetal lung ultrasound images have been attempted over the last 25 years, including gray-scale measurements,[13,14] lung tissue motion,[15,16] or the relationship between image features of fetal lung vs placental or liver tissue.[17]

These studies generally showed a good correlation with NRM, but the diagnostic accuracy was insufficient for clinical use. However, over recent years, image resolution of fetal ultrasound and computer image processing has evolved immensely.

Quantitative texture analysis is a powerful technique that can be used to extract information from medical images and to quantify tissue changes not visible to the human eye, allowing the training of computer programs that may predict clinical events.[18,19] Earlier studies reported that texture analysis can be applied to fetal lung ultrasound images and to correlate with both gestational age[20] and the results of fetal lung maturity testing of the amniotic fluid.[21] In a recent single-center study, we tested software based on quantitative texture analysis of fetal lung (quantusFLM) trained to predict NRM. The software achieved a predictive accuracy similar to

Cite this article as: Palacio M, Bonet-Carne E, Cobo T, et al. Prediction of neonatal respiratory morbidity by quantitative ultrasound lung texture analysis: a multicenter study. Am J Obstet Gynecol 2017;217:196.e1-14.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.03.016

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that commonly reported for fetal lung maturity testing of the amniotic fluid.[22]

Herein we report the results of a large multicenter study designed to evaluate the performance of quantusFLM to predict NRM. Fetal lung ultrasound images were obtained for analysis within 48 hours of delivery in a large cohort of pregnancies at 25.0−38.6 weeks of gestation. Neonatal respiratory outcomes were prospectively recorded and the performance of the software to predict NRM was analyzed.

Material and Methods

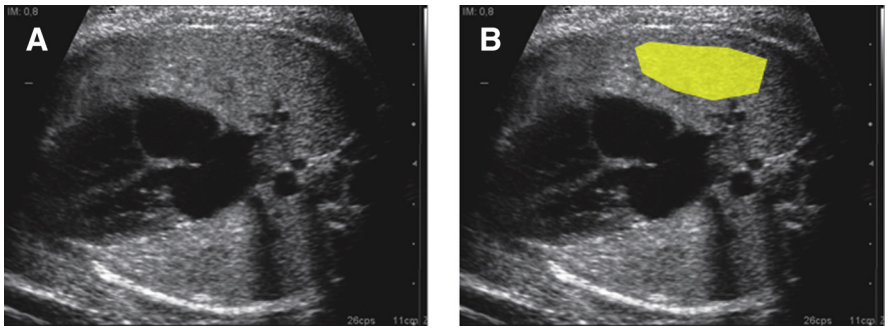
This was a prospective multicenter study involving 20 centers. Patients were recruited from June 2011 to December 2014. Eligible cases included pregnancies between 25.0-38.6 weeks of gestation and for which an ultrasound was obtained within 48 hours of delivery.

Cases were considered noneligible if corticosteroids were used for lung maturity between the ultrasound and delivery, when the maternal body mass index was $\geq$35 kg/m^2, and when fetuses had known congenital malformations. Furthermore, neonates with the following conditions were excluded: neonatal sepsis, an umbilical artery pH <7.00, hemodynamic failure, symptomatic anemia (hemoglobin <12 mg/dL), a postnatal diagnosis of structural or chromosomal abnormalities, and meconium aspiration. These conditions could directly predispose or lead to NRM, irrespective of lung maturity.

Ultrasound images were obtained following a detailed acquisition protocol. Briefly, an axial section of the fetal thorax at the level of the 4-chamber cardiac view was magnified by adjusting the depth, but not the zoom option, until the thorax occupied about two-thirds of the screen, avoiding obvious acoustic shadows from the fetal ribs (Figure 1A). Images were acquired without any type of postprocessing manipulation such as smoothing, color Doppler, or any calipers or pointers. The use of tissue harmonic imaging and adjustment of image settings such as gain, frequency, and time-gain compensation were left to the discretion of the ultrasound operator performing the ultrasound scan.

Before starting recruitment, each center submitted a minimum of 5 ultrasound images of the fetal lung that were reviewed by imaging engineers (E.B.-C. and A.P.-M.), according to this acquisition protocol, to ensure that quality criteria were fulfilled. If not, further images were requested. All study images were collected and stored in the original Digital Imaging and Communication in Medicine format and sent to the coordinator via a file transfer protocol. Digital Imaging and Communication in Medicine scans were anonymized,

FIGURE 1
Fetal lung image acquisition and delineation



A, Lateral axial transverse section of the fetal thorax at the level of the 4-chamber section of the fetal heart. **B,** Region of interest delineated.

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FIGURE 2
Flow chart of the eligible samples

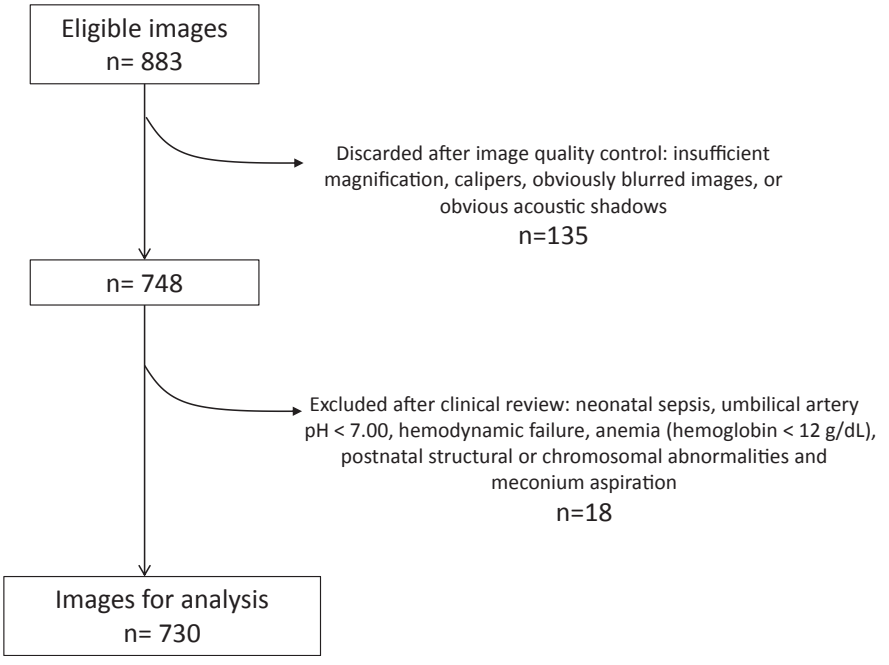

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TABLE 1
Clinical characteristics of the women included in the study

	Total (n = 685)	GA range at scan, wks (25.0–33.6) (n = 145)	GA range at scan, wks (34.0–38.6) (n = 540)
Maternal age	32.3 (5.8)	31.4 (5. 8)	31.3 (5.8)
Nulliparity	340 (49.6%)	70 (48.3%)	270 (50%)
Ethnicity			
Caucasian	400 (58.4%)	93 (64.1%)	307 (56.9%)
Black	40 (5.8%)	9 (6.2%)	31 (5.7%)
Asian	44 (6.4%)	0	44 (8.2%)
Hispanic	121 (17.7%)	24 (16.6%)	97 (18.0%)
Other	53 (7.7%)	18 (12.4%)	35 (6.5%)
Multiple pregnancy	65 (9.5%)	21 (14.5%)	44 (8.1%)
Maternal or fetal relevant conditions			
Preterm labor	48 (7%)	26 (17.9%)	22 (4.1%)
PPROM	158 (23.1%)	70 (48.3%)	88 (16.3%)
Preeclampsia	116 (16.9%)	40 (27.6%)	76 (14.1%)
IUGR	148 (21.6%)	32 (22%)	116 (21.5%)
Pregestational diabetes	15 (2.2%)	3 (2.1%)	12 (2.2%)
Antepartum hemorrhage	10 (1.5%)	3 (2.1%)	7 (1.3%)
Other[a]	160 (23.4%)	31 (21.4%)	129 (23.9%)

Data are mean (SD) or n (percentage) when appropriate.

GA, gestational age; *IUGR*, intrauterine growth restriction; *PPROM*, preterm premature rupture of membranes.

[a] Hypothyrodism, hypertensive disorders, placenta previa, lupus, human immunodeficiency virus positive, assessment of fetal well-being, and fetal presentation.

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removing all information related to the patient.

To track the scan, a new random number was generated for each new image. Lung images for the study were then inspected for image quality control by the engineer's team and discarded if one or more of the requirements previously mentioned were not fulfilled. Images passing the quality criteria were then loaded via the Internet through a restricted access to the commercial software web site and delineated using the quantusFLM web interface (www.quantusflm.com; Transmural Biotech, Barcelona, Spain).

Delineations were performed by either the same clinicians acquiring the images at each participating center or by research clinicians at the coordinating center. Delineation of the region of interest included the largest possible area of the fetal lung proximal to the transducer, avoiding the heart and great vessels (Figure 1B). The web software contained an automatic filter to accept the delineation only when at least 400 pixels were included.

Delineated ultrasound images were then analyzed automatically with quantusFLM. Features of the software used by quantusFLM have been described in detail elsewhere.[22] The software contains algorithms that analyze the textural patterns of the delineated area in the ultrasound image. These algorithms have been trained by means of a machine learning approach to estimate the probability of NRM, using hundreds of cases of fetal lung ultrasound images in which the occurrence of NRM was known.

The software used in this study utilizes different sequences of texture features adapted to gestational age ranges.[16] Therefore, gestational age in weeks was not used to calculate any a priori risk of NRM but to decide the specific algorithm used to calculate the probability of NRM. The software used in this study provided categorical results (ie, either high or low risk for NRM).

For each recruited case, the centers prospectively recorded the maternal baseline characteristics and the neonatal outcomes in a database purposely designed for this study. Anonymized clinical information from each case was submitted to the coordinator through a customized file transfer protocol and stored in a database available only to the clinical researchers of this project (M.P. and T.C.), who confirmed eligibility criteria and the absence of exclusion criteria for each case. Analysis of neonatal clinical information was supervised by a neonatologist (F.B.). The study protocol was approved by the coordinator's Institutional Review Board (2011/6291, 2013/8892).

TABLE 2
Perinatal and neonatal outcomes of the newborns included in the study

Variables	Total (n =730)	Gestational age at scan, wks (25.0–33.6) (n = 164)	Gestational age at scan, wks (34.0–38.6) (n = 566)
Gestational age at delivery, wks	36.0 (2.6)	31.4 (2.2)	37.2 (1.2)
Ultrasound-to-delivery lapse of time, d	0.6 (0.7)	0.7 (0.7)	0.6 (0.6)
Mode of delivery			
Spontaneous vaginal delivery	294 (40.3%)	50 (30.5%)	244 (43.1%)
Operative vaginal delivery	48 (6.6%)	4 (2.4%)	44 (7.8%)
Nonelective cesarean delivery	125 (17.1%)	36 (22.0%)	89 (15.7%)
Elective casarean delivery	263 (36.0%)	74 (45.1%)	189 (33.4%)
Birthweight, g	2517 (760)	1554 (486)	2796 (575)
Female sex	365 (50.0%)	70 (42.7%)	295 (52.1%)
Apgar at 5 min <7	10/729 (1.4%)	7/163 (4.3%)	3/566 (0.5%)
pH UA 7.00 to <7.10	18/479 (3.8%)	5/124 (4%)	13/355 (3.7%)
Hyperbilirrubinemia (phototherapy)	152 (20.8%)	86 (52.4%)	66 (11.7%)
Other relevant conditions			
Apnea	20 (2.7%)	20 (12.2%)	0
Bronchopulmonary displasia	8 (1.1%)	8 (4.9%)	0
Persistent pulmonary hypertension	3 (0.4%)	2 (1.2%)	1 (0.2%)
Intraventricular hemorrhage (III or IV)	3 (0.4%)	3 (1.8%)	0
Necrotizing enterocolitis	3 (0.4%)	3 (1.8%)	0
Neonatal death <28 days	3 (0.4%)	3 (1.8%)	0
NICU admission	242 (33.2%)	148 (90.2%)	94 (16.6%)
Length of stay at NICU	18.7 (19.5)	25.5 (21.4)	8.2 (9.0)
Discharged alive from NICU	239/242 (98.8%)	145/148 (98.0%)	94/94 (100%)

Data are mean (SD) or n (percentage) when appropriate.

UA, umbilical artery; *NICU*, neonatal intensive care unit.

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Patients included in the study received care in the participating institutions and were enrolled in a specific protocol for the evaluation of fetal lung maturity, in studies involving the use of fetal ultrasound, or in studies in which ultrasound was used as part of the clinical management approved by the local review boards. All patients included gave written informed consent for the use of ultrasound images and perinatal data. None of the observations reported here has been previously used in another study.

The primary clinical outcome of the study was NRM, including respiratory distress syndrome (RDS) or transient tachypnea of the newborn. Respiratory distress syndrome was defined based on clinical criteria, including grunting, nasal flaring, tachypnea, and chest wall retraction, or the need for supplemental oxygen together with typical chest radiography findings and admission to the neonatal intensive care unit for respiratory support.[2] Transient tachypnea of the newborn was diagnosed based on early respiratory distress (isolated tachypnea, rare grunting, minimal retraction) and a chest X-ray showing hyperaeration of the lungs and prominent pulmonary vascular patterns.[23]

The performance of quantusFLM to predict NRM was analyzed by the clinical researchers of this project (M.P. and T.C.) by matching quantitative ultrasound analysis and clinical outcome. Descriptive statistical methods were used to summarize the distribution of all the variables; for continuous variables, mean and SD values were obtained; and, for categorical variables, frequencies and percentages were reported. Descriptive statistics were performed with R language (R Foundation for Statistical Computing, Vienna, Austria, 2015; https://www.R-project.org).

Results

A total of 883 cases were recruited. Of these, 135 (15.3%) were excluded after

TABLE 3
Characteristics of the respiratory support and respiratory morbidity

Characteristics	Total (n = 730)	Gestational age at scan, wks (25.0–33.6) (n = 164)	Gestational age at scan, wks (34.0–38.6) (n = 566)
Need for respiratory support (any)	115 (15.8%)	89 (54.3%)	26 (4.6%)
Oxygen therapy ≥40%	55 (7.5%)	37 (22.6%)	18 (3.2%)
CPAP	117 (16%)	94 (57.3%)	23 (4.1%)
NIV/BPAP	23 (3.2%)	22 (13.4%)	1 (0.2%)
Intubation required	31 (4.3%)	28 (17.1%)	3 (0.5%)
Days of intubation (if any)	6 (9.4)	6.7 (9.9)	1.8 (1.5)
High-frequency ventilation	12 (1.6%)	10 (6.1%)	2 (0.4%)
Surfactant use	34 (4.7%)	32 (19.5%)	2 (0.4%)
Doses of surfactant (if any)	1.4 (0.7)	1.4 (0.7)	2 (1.4)
Neonatal respiratory morbidity	101 (13.8%)	72 (43.9%)	29 (5.1%)

Data are mean (SD) or n (percentage) when appropriate.

CPAP, continuous positive airway pressure; *NIV/BPAP*, noninvasive ventilation/bilevel positive airway pressure.

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image quality control and 18 (2.0%) were excluded because of 1 or more clinical exclusion criteria (42 of 164, 25.6%, in the 25–33.6 weeks group and 111 of 566, 19.6%, in the 34.0–38.6 weeks group), leaving a total of 730 images for analysis (Figure 2). The final number of cases included per center and the ultrasound equipment locally used are described in the supplemental material (Supplemental Tables 1 and 2).

The clinical characteristics of the pregnant women enrolled in the study and the relevant conditions for which ultrasound was indicated are detailed in Table 1. The study included the following: 17 women (2.5%) at <28 weeks; 128 women (18.7%) at 28.0 to <34.0 weeks of gestation; 176 women (25.7%) at 34.0 to <37.0 weeks of gestation; and 364 women (53.1%) at ≥37.0 weeks of gestation. Perinatal and neonatal outcomes and the

TABLE 4
quantusFLM performance to predict neonatal respiratory morbidity

Characteristics	Total (n = 730)	Geatational age, wks (25.0–33.6) (n = 164)	Geatational age, wks (34.0–38.6) (n = 566)
Neonatal respiratory morbidity	101 (13.8%)	72 (43.9%)	29 (5.1%)
True positives	75	57	18
True negatives	557	67	490
False positives	72	25	47
False negatives	26	15	11
Accuracy	86.6% (632/730)	75.6% (124/164)	89.8% (508/566)
Sensitivity	74.3% (75/101)	79.2% (57/72)	62.1% (18/29)
Specificity	88.6% (557/629)	72.8% (67/92)	91.3% (490/537)
Positive predictive value	51% (75/147)	69.5% (57/82)	27.7% (18/65)
Negative predictive value	95.5% (557/583)	81.7% (67/82)	97.8% (490/501)
Positive likelihood ratio	6.5	2.9	7.1
Negative likelihood ratio	0.3	0.3	0.4

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TABLE 5
Summary of performance of invasive tests in amniotic fluid used to predict neonatal respiratory morbidity (summarized from Table 3S)

	Ac	Se	Sp	PPV	NPV
quantusFLM	86.5%	74.3%	88.6%	51%	95.5%
L/S	81.6%	74.6%	82.5%	34.1%	96.4%
PG	57.5%	82.7%	54.4%	18.0%	96.3%
LBC	75.4%	84.2%	74.4%	27.9%	97.6%
TDxII	78.7%	88.5%	77.7%	28.5%	98.5%

Ac, accuracy; *L/S*, lecithin/sphingomyelin ratio; *LBC*, lamellar body count; *NPV*, negative predictive value; *PG*, phosphatidylglycerol; *PPV*, positive predictive value; *Se*, sensitivity; *Sp*, specificity; *TDxII*, surfactant/albumin ratio.

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characteristics of the respiratory support are shown in Tables 2 and 3, respectively.

The prevalence of NRM was 13.8% (101 of 730), of which 66.3% (67 of 101) were diagnosed as RDS and 33.7% (34 of 101) as transient tachypnea of the newborn. All newborns diagnosed with RDS were treated with at least 1 of the following: oxygen higher than 40%, continuous positive airway pressure, or noninvasive ventilation, high-frequency ventilation and an endotracheal tube for invasive ventilation, or surfactant use.

The quantusFLM analysis predicted the occurrence of NRM with a sensitivity, specificity, positive predictive value, and negative predictive value of 75 of 101 (74.3%), 557 of 629 (88.6%), 75 of 147 (51.0%), and 557 of 583 (95.5%), respectively. Accuracy was 86.6% (632 of 730), and the positive and negative likelihood ratios were 6.5 and 0.3, respectively. The predictive performance stratified by gestational age is shown in Table 4.

Comment

Principal findings of the study

The main finding of this large multicenter study is that quantitative texture analysis of fetal lung ultrasound images predicted NRM with a similar accuracy to that of laboratory tests using amniotic fluid, which have reported sensitivities and specificities ranging from 74% to 89% and from 54% to 89%, respectively,[9,24,25] although a wide range of figures has been reported (Table 5 and Supplemental Table 3). Furthermore, the risk of respiratory neonatal morbidity observed in this study was similar to that reported in a large cohort study including late preterm and early term infants recently published (Supplemental Table 4).

Results of the study in the context of other observations

Several attempts have been made to predict fetal lung maturity using ultrasound images. Serizawa and Maeda[13] and Maeda et al[14] compared the ultrasonic gray-level histogram width of the fetal lung and liver, while Bhanu Prakash et al[17] compared the values for the fetal lungs to those of the liver. La Torre et al[16] correlated several patterns of fetal breathing movements with fetal lungs maturity tests, and Tekesin et al[26] evaluated the mean gray value of fetal lungs.

The accuracy identifying NRM in all these studies has ranged from 73% to 96%. However, no prospective studies have been conducted after them to validate the associations observed (Supplemental Table 3). The approach used in this study was different from previous attempts to noninvasively assess fetal lung maturity.

The method used herein is based on the combination of texture extraction with machine learning methods, allowing the identification of texture patterns in the ultrasound image that correlate with the clinical outcome. This approach has been shown to be reliable and robust to small variations in the conditions of the image acquisition, including depth and changes in the gain of the image and does not need other tissues with which to be compared (placenta, fetal liver, …).[20] In addition, a previous pilot study reported on the ability of this noninvasive technology to predict NRM.[22]

Clinical implications

Liggins and Howie[27] stated that the use of antenatal corticosteroids could enhance fetal lung maturity in preterm pregnancies; as a result, corticosteroid use is common practice with pregnancies up to 34 weeks of gestation.[28-30] Now the question as to whether late preterm fetuses may benefit from such an intervention is on the rise.

The practice of testing for fetal lung maturity is extremely variable worldwide, being widely used in some areas and completely ignored in others. Estimation of fetal lung maturity might reduce the use of corticosteroids in late preterm deliveries (34−36 weeks of gestation), for which the risk of NRM is relevant but relatively low, ranging from 10% to 20%.

As recently shown, steroids decrease by one-third the occurrence of NRM in late preterm deliveries,[8,31-34] and the number needed to treat to reduce one case of NRM in the circumstances described is 25.[8] These findings have resulted in the publication of a Society for Maternal-Fetal Medicine statement on the use of antenatal corticosteroids in the late preterm period[35]; it recommends treatment under the strict inclusion criteria of the Antenatal Late Preterm Steroids study, while warns against overtreatment in those cases that do not meet the inclusion criteria.

Even if mid- and long-term follow-up of babies exposed to corticosteroids has shown no adverse effects or no benefits in some studies,[36-39] antenatal corticosteroids might be associated with potential side effects related to overexposure later in life,[40-42] particularly in those babies who will be delivered at term.[43,44] A substantial proportion of fetuses treated with corticosteroids are delivered long after 1 week of the initial dose or even at term.[45-50] Rescue doses are debatable,[51,52] and the benefits and risks have to be evaluated when repeated

doses are considered long after an initial course was given early in pregnancy[53-55] or if an early term elective cesarean delivery is planned.[56] Thus, strategies to define the target population are urged.

On the other hand, the fear of overtreatment has to be counterbalanced against the fact that restrictive messages may limit the use of corticosteroids in those cases for which the intervention has been proven to be of benefit and for which additional information from quantusFLM is of limited value (ie, preterm delivery at <32 weeks). For instance, some data showed that among cases with potential benefit, only 80% received one dose and 70% received two doses.[57] On the contrary, there are other studies reporting that a wide use of corticosteroids might not be of benefit in all countries.[58]

All these aspects have been discussed in recent reviews; therefore, the issue remains controversial.[59,60] It is in this context that the selection of a low-risk group for respiratory morbidity by a noninvasive tool might reduce exposure in a large number of pregnancies, avoiding the risks of overexposure in an unselected population and optimizing intervention in those cases for which it is needed.

Additionally, a common argument against testing for fetal lung maturity is that there is or is not a clear indication for elective preterm delivery and therefore, the results of fetal lung maturity testing would not be of help.[4,61] This view might be challenged by studies reporting that about 23% of late-preterm deliveries had no clear indication for delivery[62] or that they were delivered after a non-evidence-based indication.[63] Therefore, a fraction of complicated pregnancies may fall within a gray zone, for which elective delivery may be considered as an option when there is not a strict indication according to clinical protocols or guidelines.[64] In these cases, information about fetal lung maturity might be of help to plan delivery.

Likewise, access to advanced neonatal care is not readily available in all clinical settings, even in high-resource countries. In these circumstances, knowing the risks of respiratory morbidity with an acceptable accuracy might help clinicians and parents to make more balanced decisions and/or to determine the most appropriate place for delivery.[65]

Finally, among the reasons for avoiding fetal lung maturity testing may be the fear for complications of amniocentesis, reported to occur in 0.7% of cases[66,67] as well as medical costs and/or maternal discomfort. This perception and, consequently, the attitude of physicians and parents seeking information about fetal lung maturity might be reconsidered if this information can be obtained with a noninvasive test.

Strengths and limitations

The results of this multicenter study are in line with those obtained in a previous smaller study in which the technology was prospectively and blindly evaluated in a single center in 144 patients.[22] These findings and the multicenter nature of the study support the fact that, provided the quality criteria in the acquisition of the images are respected, the test is robust and yields similar performances in different clinical settings, enhancing the likelihood that results are generalizable.

However, this study has some limitations. The method tested in this study uses an indirect approach to estimate lung maturity. By definition, prenatal prediction of NRM is hampered by the fact that the outcome is largely, but not exclusively, determined by the fetal lung maturity status. Thus, in circumstances such as neonatal sepsis, congenital anomalies potentially affecting lung function, or intrapartum hypoxic-ischemic events, newborns with normal lung maturity in utero may present respiratory impairment. Also, specific conditions such as fetal growth restriction, multiple pregnancy, diabetes, or premature rupture of the membranes were not analyzed separately. Differences in the performance of quantusFLM in these subgroups cannot be excluded and requires further research.

On the other hand, the performance of the software for each specific gestational age was not assessed in this study because the algorithms were not designed to predict NRM for each specific gestational age. Future algorithms with 1- or 2-week gestational age intervals would be more precise, although whether this could improve the accuracy reported herein remains to be assessed.

Regarding the mode of delivery, the rate of cesarean section was high, around 50%. This is due to the fact that to meet inclusion criteria, delivery had to occur within 48 hours of the image acquisition. Therefore, planned cesarean sections might be overrepresented in our study population although this rate could be comparable to some settings. Besides, according to clinical practice, elective and no-elective cesarean deliveries are more frequent in preterm pregnancies.

Finally, despite that the ultrasound image required to perform the test was an axial section of the thorax, considered as a standard section, a relatively high number of images were eventually discarded because of the lack of compliance with the quality criteria requisites. This stresses the fact that obtaining a valid ultrasound axial section of the fetal thorax at late gestation might not always be straightforward, and in particular cases, the test might require special care or training to ensure an optimal image acquisition.

Conclusion

In summary, the results of this large multicenter study are consistent with the findings of a pilot study on the ability of a noninvasive technology to predict NRM from fetal lung ultrasound images.[22] The technology also showed an accuracy similar to that of biochemical tests in amniotic fluid previously reported. Therefore, quantusFLM provides a noninvasive tool that might help clinicians in the decision-making process. ■

Acknowledgment

The Fetal Lung Texture Team includes the following collaborators: Montse Palacio, Teresa Cobo, Marta López, Dulce Castro, Juan Pablo Piraquive, Juan Carlos Ramírez, Federico Migliorelli, Mónica Martínez-Terrón, Francesc Botet, Eduard Gratacós (BCNatal Hospital Clínic, Barcelona, Spain); Joan Sabrià, Silvia Ferrero Martínez, Dolores Gómez Roig (BCNatal Hospital Sant Joan de Déu, Barcelona, Spain); Elisenda Bonet-Carné, Àlvaro Pérez, Mara

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Received Dec. 23, 2016; revised Feb. 23, 2017; accepted March 15, 2017.

M.P., T.C., J.D., and E.G. have served as scientific advisers to Transmural Biotech. The other authors report no conflict of interest.

The work of Dr. Romero was supported by the Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS) and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C. Dr. Romero has contributed to this work as part of his official duties as an employee of the U. S. federal government.

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SUPPLEMENTAL TABLE 1
Number of images included in each center

Center	n = 730	%
BCNatal (Spain)	182	24.9
UZ Leuven (Belgium)	77	10.5
Hradec Kralove (Czech Republic)	64	8.8
Sahlgrenska University Hospital (Sweden)	48	6.6
Clínica el Prado Medellin (Colombia)	47	6.4
Hospal University Puerta del Mar (Spain)	44	6.0
Althaia (Spain)	40	5.5
Consorci Sanitari Terrassa (Spain)	40	5.5
University of Chile Hospital Chile (Chile)	33	4.5
Perinatology Research Branch (United States)	33	4.5
Hospital La Paz (Madrid)	28	3.8
Hospital San Cecilio (Spain)	25	3.4
KK Women's and Children's Hospal (Singapore)	23	3.2
Children's and Women's Specialty Hospital of Queretaro (Mexico)	14	1.9
Royal Prince Alfred Hospital (Australia)	12	1.6
Fernandez Hospital (India)	8	1.1
University of Wisconsin (United States)	4	0.6
Hospital Virgen Arrixaca (Spain)	4	0.6
UTHSC (United States)	2	0.3
Hospital Nostra Sra Meritxell (Andorra)	2	0.3

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SUPPLEMENTAL TABLE 2
Ultrasound equipment used in the study in alphabetical order

Equipment	n = 730	%
Aloka		
Aloka 4000	33	4.5
General Electrics		
Voluson 730	214	29.3
Voluson E6	56	7.7
Voluson S6	45	6.2
Voluson E8	123	16.8
Voluson P8	8	1.1
Samsung		
Medison	12	1.6
Siemens		
Acuson Antares	148	20.3
Toshiba		
Aplio	64	8.8
Nemio	2	0.3
Xario	25	3.4

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SUPPLEMENTAL TABLE 3

Diagnostic performance of non-invasive and invasive tests in amniotic fluid used to predict neonatal respiratory morbidity

	N	Ac	Sen	Sp	PPV	NPV
Noninvasive tests						
Gray-level histogram[13,14]	22/47	—	86	72	—	—
Fetal breathing movements[15,16]	—/43	—	92	85	92	80
Liver-to-lung texture[17]	750/1000 73-96	—	—	—	—	
quantusFLM[22]	29/144	86	86	87	62	96
quantusFLM (present study)	101/730	86	74	88	51	95
Invasive tests[25,68-72]						
Lecitin/esphingomielin ratio						
Bowie	5/52	85	80	85	36	98
Ashwood	17/187	84	82	85	35	98
Dalence	12/122	89	92	89	48	99
Fakhoury	4/28	96	75	100	100	96
Greenspoon	7/70	80	71	81	29	96
Lee	14/141	92	64	95	60	96
Karcher	13/201	88	62	89	29	97
Hagen	29/140	81	48	89	54	87
Rusell	23/294	84	96	83	32	100
Neerhof	100/833	76	81	76	32	96
Phosphatidilglicerol						
Karcher	13/204	69	92	67	16	99
Hagen	21/113	73	86	71	40	96
Rusell	16/240	80	94	79	24	99
Neerhof	100/833	47	80	42	15	94
Lamellar bodies count						
Bowie	8/56	75	88	73	35	97
Ashwood	28/247	91	71	93	57	96
Dalence	16/130	96	75	99	92	97
Fakhoury	4/28	100	100	100	100	100
Greenspoon	7/62	90	100	89	54	100
Lee	14/157	94	79	95	61	98
Karcher	13/219	76	85	75	18	99
Haymond	12/184	62	92	60	14	99
Neerhof	100/833	66	88	63	25	97
TDxII-FLM						
Karcher	13/218	78	92	78	21	99
Haymond	12/194	66	83	65	14	98
Hagen	29/140	77	90	74	47	100
Rusell	24/301	89	96	88	42	100

The outcome generally tested was RDS.

Ac, accuracy; *n*, RDS/total; *NPV*, negative predictive value; *PPV*, positive predictive value; *RDS*, respiratory distress syndrome; *Sen*, sensitivity; *Sp*, specificity.

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SUPPLEMENTAL TABLE 4

Prediction of neonatal respiratory morbidity by gestational age at 34.0–38.6 weeks

GA threshold, wks	≥34	≥35	≥36	≥37	≥38
True positives	0	390	719	1002	1206
True negatives	80,221	76,911	71,763	61,889	41,624
False positives	0	3310	8458	18332	38597
False negatives	1346	956	627	344	140
Accuracy	98%	95%	89%	77%	53%
Sensitivity	0%	29%	53%	74%	90%
Specificity	100%	96%	89%	77%	52%
Positive predictive value	0%	11%	8%	5%	3%
Negative predictive value	98%	99%	99%	99%	100%

Data are extracted from Hibbard et al[2] (n = 81,567, NRM, n = 1346). All figures are numbers or percentage where stated.

GA, gestational age at delivery.

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