Full length article

Fetal lung maturity assessment: A historic perspective and Non – invasive assessment using an automatic quantitative ultrasound analysis (a potentially useful clinical tool)

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ABSTRACT

Immature fetal lung is associated with many adverse outcomes including respiratory distress syndrome and transient tachypnoea of the newborn. Several methods/tools have been used over several decades to assess fetal lung maturity prior to delivery. Some of the methods that have been used to assess fetal lung maturity include amniocentesis for the biochemical markers, lecithin and sphingomyelin, lamellar body counts, gray scale ultrasound scan and magnetic resonance imaging. Amniocentesis an invasive procedure which carries a small risk of miscarriage has almost become obsolete. Magnetic resonance imaging on the other hand is expensive and not very practical.

Quantitative ultrasound fetal lung maturity (quantusFLM) assessment is a new technique aimed at assessing fetal lung texture using ultrasound. The technique depends on visualization of fetal lungs at the level of the 4- chamber view. Images obtained are then uploaded via a web page application and these are analyzed remotely and results generated in minutes. The analysis depends on studying changes in the texture of lung images that depend on changes at histological level especially of collagen, fat and water. These changes are undetectable to the human eye. Randomized clinical trials have shown this technique to be accurate, reproducible, and completely non – invasive.

The aim of this review was to take a historic look at methods/tools for assessing fetal lug maturity and discuss further advances and a potential non-invasive tool/method especially the non-invasive assessment that combines ultrasound scan and machine learning to accurately assess lung maturity.

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Introduction

The development of the fetal lung is divided into five stages the (i) Embryonic covering the period up to 7 weeks, (ii) Pseudoglandular covering the period 7–16 weeks, (iii) Canalicular covering the period 16–25 weeks, (iv) Saccular covering weeks 25–36 and (v) Alveolar covering weeks 36−38. It is usually at the end of the Canalicular stage that epithelia differentiation occurs, with type II pneumocytes differentiating to type I and lamellar bodies (in which surfactant synthesis begins by 20 weeks) forming in type II pneumocytes. By the end of this period, the preterm lung is potentially viable [1]. The presence of amniotic fluid is critical to the development of fetal lungs especially for the 2nd and 3rd stages. Anhydramnios before the 20nd week of gestation is associated with pulmonary hypoplasia that is unlikely to support extra-uterine survival, but when it occurs after the onset of surfactant production, the lungs may be able to support the neonate [2]. It is important to remember other causes of pulmonary hypoplasia, examples of which are (to mention a few) congenital diaphragmatic hernia, some forms of skeletal dysplasia associated with a narrow chest, congenital cardiac malformations and cysts in the lungs and pleural effusion. While lung development continues into the late third trimester (the Alveolar stage), a significant number of babies are delivered well before this period.

In considering the timing of delivery especially of high-risk pregnancies, an important factor to take into account is lung maturity. Immature fetal lungs are associated with significant neonatal morbidity in the form of respiratory distress syndrome or transient tachypnoea of the newborn [3,4]. Assessing fetal lung maturing would be significantly beneficial in the timing of delivery of high-risk pregnancies in order to minimize the associated perinatal morbidity and mortality with immature lungs.

Neonatal respiratory distress syndrome (RDS) first described in 1959 by Avery and Mead [5] is characterized by a compromised respiration presenting at or shortly after delivery. It is due to a

deficiency in pulmonary surfactant produced by type II pneumo-cytes, whose function is to reduce surface tension within the alveoli and thereby prevent alveolar collapse. It is estimated to complicate about 1% of all live births but more common for deliveries before 34 weeks of gestation [6,7]. For babies weighing less than 2500 g, it complicated 10–15 %, with iatrogenic prematurity responsible for 10–20 % of these. While the use of corticosteroids has significantly reduced the incidence of RDS in preterm births, babies born after 35 are still at risk of RDS especially those born by elective caesarean section (CS). The estimated risk ratio of composite neonatal morbidity which is inclusive of RDS and persistent pulmonary hypertension is 1.74 (95 % CI 1.1–2.8) for Caesarean sections between 37°-37^6 weeks compared to delivery at 38°-38^6 weeks and 2.4 (95 % CI 1.2–4.8) between 38°-38^6 weeks compared to delivery at 39°-39^6 weeks [8].

The satisfactory assessment of fetal lung maturity can potentially help in reducing the need for corticosteroids to enhance fetal lung maturity and also refine the timing of delivery in high risk pregnancies. Antenatal corticosteroids are used extensively to enhance fetal lung maturity. These are not without risks, and are capable of affecting both the neonate and the mother. The neonates are at risk of hypoglycaemia and long-term cardiometabolic and neurological development [9–12]. A recent population - based study conducted in Finland involving more than 250,000 infants showed that the use of antenatal corticosteroid is associated with a reduction in the infant birth size [13].

In this article we review the various approaches that have been used to assess fetal lung maturing historically and a contempora-neous non-invasive approach which is most likely to be refined and eventually become part of fetal lung assessment prior to the preterm or elective delivery of high-risk pregnancies.

Historic approaches to assessing fetal lung maturity

Amniocentesis

Direct assessment of fetal lung maturity is hampered by access. Following the discovery of the lecithin/sphingomyelin (LS) ratio by Gluck et al. [14] this became the gold standard for fetal lung assessment for many years. The rationale for this test was that biochemical changes in the amniotic fluid reflected lung maturity and thus the basis for various tests on amniotic fluid for lung maturity. The cut-off L/S ratio of 2 was based on the fact that after 32–33 weeks of gestation, lecithin but not sphingomyelin increases in the fetal lung and a ratio of at least 2 is reached by 35 weeks when RDS is less likely to happen. As a thin layer chromatography assay it took 4 h for the result to be generated [15]. Other tests on amniotic fluid included measurement of phosptatidylglycerol (whose presence indicates fetal lung development and function) [16]. Phosptatidylglycerol increases significantly in amniotic fluid several weeks after the rise in lecithin. This was not as widely used as the L/S ratio even though blood did not affect the result but affected the L/S test. The surfactant-to-albumin ratio performed by the TDX FLM II assay, quantified the binding of a probe to both albumin and surfactant – expressed as milligrams of surfactant/gram of albumin. An elevated ratio correlates with lung maturity with a value of 55 mg/g being considered the threshold; a measure of 40 mg/g indicates immature lungs and 40–54 mg/g borderline [17]. The Shake Test [18] and the Foam Stability Index (FSI) [19] are biophysical tests that were used to assess the functionality of surfactant. The Shake Test described by Clemens et al. in 1972 involves adding amniotic fluid to 95 % alcohol and shaking it; if a ring of bubble was present at the meniscus then the lungs were matured [18]. The foam stability index (FSI) was a refinement of the Shake test. Here 0.5 mls of amniotic fluid is added to wells of a test

kit containing serial dilutions of ethanol with the final dilution of 42 %–55 %. The mixture is then shaken for 30 s and allowed to rest for 15 s. The appearance of a stable ring of foam at over 47 % or more ethanol volume is reflective of the presence of surfactant and thus lung maturity. This test is affected by the presence of blood and meconium. The test kit was discontinued in 1997 [20].

Physical testing of the amniotic fluid opacity was also used as indirect markers of lung maturity. Under this category were the turbidity of the amniotic fluid test. Turbid amniotic fluid or one through which a newsprint could not be read was considered reflective of fetal lung maturity [21]. To improve on the subjectivity of this test, Sbarra and colleagues [22] used optical density of amniotic fluid at 650 nm and showed that when the OD was > = 0.15, the L/S ratio was always >2. This test was not affected by the presence of blood or meconium. The lamellar body count (LBC) was a test to measure surfactant production by type II pneumocytes [22]. As lamellar bodies are similar in size to platelets, these could be measured by using a standard Coulter counter. Counts of 15,000/ul represented an immature fetal lung while values >50,000/ul reflected a mature fetal lung and values of 15,000–50,000 represented an borderline fetal lung and those with such values then needed an L/S ratio before proceeding with delivery [23,24].

While amniocentesis (performed from 24 to 34 weeks of gestation in most cases, and up to 37 weeks of gestation in some) provides reliable and useful tools for assessing fetal lung maturity, it is associated with complications such as premature rupture of fetal membranes, chorioamnionitis, placental abruption and feto-maternal haemorrhage. At the time that amniocentesis was popularized, most of the advances in fetal imaging were not available including routine ultrasound dating of pregnancies. The use of amniocentesis for fetal lung maturity has virtually disappeared in Europe and it appears to also becoming obsolete in most parts of the USA except for use in the rare cases of elective delivery where dating of the pregnancy is poor [25].

Ultrasound evaluation of fetal lungs

With the widespread use of ultrasound in obstetrics several attempts have been made to evaluate fetal lung maturity non-invasively. As early as early as 1969, Campbell, used biparietal diameter to predict fetal lung maturity [26]. Shah et al. [27] examined the placenta grade as an indirect means to assess lung maturity and showed that none of the fetuses with grade 3 [28] placenta had RDS. Ten years later Podobnik et al. in 1996 investigated gray scale coefficient of variation of fetal lungs, placentas and livers to predict lung maturity [29]. Kim and colleagues showed that a measured elevated acceleration-to-ejection time ratio of the fetal pulmonary artery Doppler was significantly associated with neonatal RDS and thus a possible marker of lung maturity [30]. Other imaging approaches that have been investigated in assessing fetal lung maturity using conven-tional B-scan ultrasound include the thoracic circumference, lung length and ratio of thoracic to abdominal circumference [31–33]. Unfortunately none of these have been found to be sensitive enough for use to help clinical decision making with regards to the timing of delivery of high-risk pregnancies to minimize the risk of RDS. More recently attempts to quantify fetal lung volume in normal pregnancies by using 3-dimensional ultrasonography though useful in cases like diaphragmatic hernia have not been shown to objectively assess fetal lung maturity [34–39].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has also been used to assess fetal lungs. Echo-planar MRI has been used to quantify lung volume

cross-sectionally in abnormal pregnancies [40]. Duncan et al. [41] used Echo-plesplanar MRI to assess fetal lung growth during pregnancy and related it to amniotic fluid volume. While they suggested that the changes demonstrated with this technique could be useful in monitoring the effects of corticosteroids on changes in fetal lung volumes it has not been routinely applied in clinical settings to assess lung maturity prior to delivery or indeed been used to evaluate its usefulness in predicting RDS. Quantitative and qualitative evaluation of fetal lungs using MRI has, however, been shown to be useful in identify fetuses with pulmonary hypoplasia. Osada et al. [42] concluded from their studies that "there is the need for future prospective studies of the use of MRI images to predict severe respiratory disturbance in patient subgroups with specific intrathoracic congenital diseases such as diaphragmatic hernia and oligohydramnios". Despite these suggestions, this approach has not been applied in clinical practice to assess fetal lung maturity to help in planning delivery of high-risk pregnancies.

Magnetic resonance spectroscopy is another approach that has been investigated and measures the lipid component of the amniotic fluid non-invasively. However, this technique is not an attractive option at present because it is expensive, can cause maternal discomfort during acquisition and fetal movement can affect the images [43]. The introduction of a new non – invasive method for the assessment of fetal lung maturity will be a very welcome development because of the limitations of the current methods.

Assessment of fetal lung maturity using an automatic quantitative ultrasound fetal lung maturity assessment (QuantusFLM)

For several decades, ultrasound has been proposed as a possible tool for the assessment of fetal lung maturity. This has been applied to gray measurement [44], fetal lung tissue motion assessment [45], and assessment of fetal lung images relative to fetal liver and fetal placental images [46]. The diagnostic accuracy of this was unfortunately poor and therefore was not found to be of clinical value.

Quantitative ultrasound fetal lung maturity is a new technique aimed at assessing fetal lung texture using ultrasound (quantusFLM). The objective is to predict fetal lung maturity and subsequently fetal respiratory morbidity. This has become possible because of developments in two areas, (i) image resolution and (ii) computer capacity [47]. Fetal lung images are obtained by ultrasound at the level of 4- chamber heart view (Fig. 1).

Subsequently, these images are analyzed using a computed method which can detect textural changes of lung images that are invisible to the human eye [48]. Using gray scale US, the fetal lung is visualized at the level of the four chambers heart view (Fig. 1). The region of interest (ROI) - is defined in the fetal lung and delineated by the operator. The information on the fetal lung is obtained in pixels. These images are then uploaded via a web-based application. These US images of the fetal lung are analyzed at a remote center and reliable results are obtained within minutes. Ultrasound image reconstruction depends on detection of changes occurring at the histological level which include collagen, fat, water and other substances. These various structures affect the ultrasound signal of the fetal lung. As earlier mentioned, these computerized quantitative ultrasound analyses detect extremely subtle changes not seen with the naked eye. These lung images display certain features that correlate well with the fetal gestational age or the result of FLM determined by examination of the amniotic fluid [49,50].

Potential clinical use of QuantusFLM

Obstetricians are faced on a regular basis with conditions which necessitate making a decision regarding elective delivery before term for fetal or maternal indications. Before deciding on timing of iatrogenic delivery, there is the need to assess fetal lung maturity. QuantusFLM has the potential of determining fetal lung maturity before elective delivery in conditions such as severe hypertensive disorders of pregnancy, poorly controlled diabetes in pregnancy and severe intrauterine fetal growth restriction where there is no urgency in delivering either for fetal or maternal indication). QuantusFLM makes it possible to avoid using an invasive technique to predict neonatal respiratory morbidity in clinical practice. This new software, QuantusFLM, uses a cutting-edge image analysis technology that can effectively predict with accuracy the degree of fetal lung maturity (see Fig. 2). This technique was evaluated in a large prospective multicenter study. Palacio et al. studied over 800 images of fetal lung at different centers in different countries [50]. These images were taken between 25–39 weeks of gestation. All the images were analyzed with QuantusFLM. The perinatal outcome in terms of transient tachypnea of the newborn or respiratory distress syndrome were recorded. They concluded that QuantusFLM was accurate in predicting neonatal respiratory morbidity and that the accuracy of this new technique is as good as a previously prescribed invasive method of determining fetal lung maturity. The encouraging finding in this large multicentral
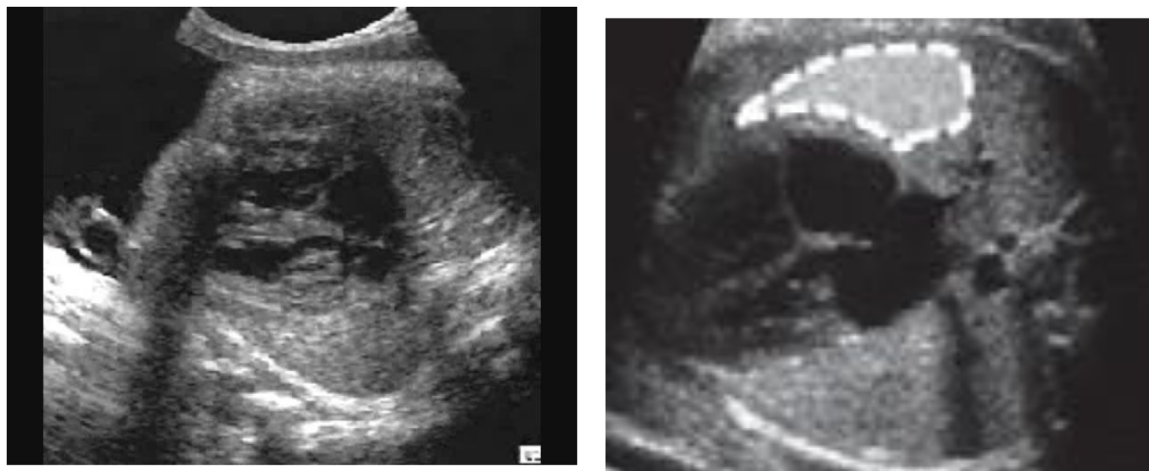

Fig. 1. The images are obtained at the level of the four-chamber view of the fetal heart. The lung is delineated using specific software. These software accept only images containing more than 400 Pixels.
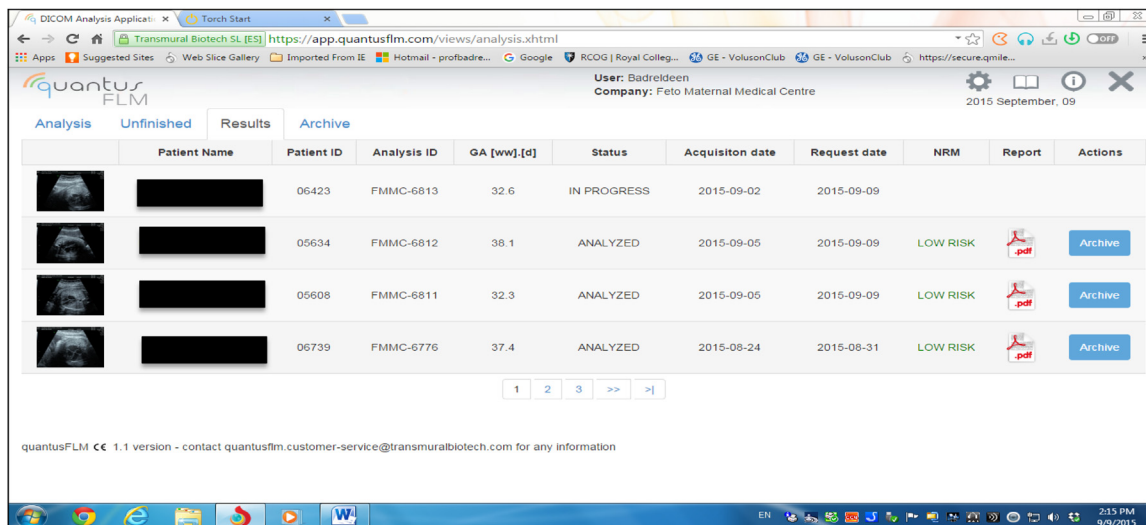
Fig. 2. An example of how the result of Quantus FML is displayed. Only high quality images are analyzed, these images have an adequate pixels. The result is reported as a high risk. Or a low risk for fetal morbidity mainly transient tachypnea and respiratory distress syndrome.

prospective study is the fact that only about 17 % of the images were discarded and deemed unsuitable for evaluation. These findings suggest that the technique can be used in any center in the world and reliable results obtained if good quality images are sent via the web. In our unit in the State of Qatar, we investigated the use of this technique in 44 cases, images were acquired after a brief orientation, passed quality assessment and were uploaded on the web and analyzed; results were obtained and we were able to access them within minutes (Unpublished data). All our patients found the technique acceptable. These helped with timing of delivery in cases where delivery was indicated but considered urgent.

This non – invasive technique has a major advantage over other techniques used for assessing fetal lung maturity. It has the potential to reduce the use of antenatal corticosteroids for fetal lung maturity. Antenatal corticosteroids are over used in most units – in ours for example, we have shown that 60 % of patients who received antenatal corticosteroids went on to deliver at term [51]. Antenatal corticosteroids can cause maternal and fetal side-effects. The use of antenatal steroids can cause intrauterine fetal growth restriction and early onset neonatal sepsis. In a large observational registered – based study in Finland, which enrolled a total of 278,508 live – born singletons at the age of 24 weeks gestation or above, the author showed that antenatal steroid is associated with the delivery of small fetus at birth [52].

Table 1 shows comparative sensitivities, specificities, positive and negative predictive values of some of the tests that have either historically or currently being used for fetal lung maturity assessment. QuantusFLM system is accurate, reproducible and relatively simple to use; as non- invasive and causing no discomfort to patients it would be more acceptable to patients. While these findings from the early studies are very encouraging, there is a need for further evaluative studies of this potentially useful clinical tool.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1

Comparison of Sensitivities, specificities, negative and positive predictive values of some of the historical and/or currently used tests for fetal lung maturation.

Test	Sensitivity	Specificity	Negative Predictive value (NPV)	Positive Predictive value (PPV)	Reference
Gestational age only	88.8 %	73.5 %	97.7 %	34.45	
Amniocentesis (L/S ratio)	74.6 %	82.5 %	96.4 %	34.1 %	Palacio et al. [50]
Amniocentesis (phosphatidyl – glycerol)	82.7 %	54.4 %	96.3 %	18.0 %	Palacio et al. [50]
Amniocentesis (Surfactant/Albumin ratio)	88.5 %	77.7 %	98.5 %	28.5 %	Palacio et al. [50]
Amniocentesis (Rapid visual test)	90.8 %	70.3 %	N/A	N/A	Sbarra et al.
Foam stability test	87 %	54 %	92 %	42 %	Taborda et al.
Lung profile	100 %	76 %	100 %	61 %	Taborda et al.
Lamillar body count	84.2 %	74.4 %	97.6 %	27.9 %	Palacio et al. [50]
Lung-liver signal intensity	100 %	73 %	N/A	N/A	Oka et al.
(Pulmonary artery Doppler wave acceleration/ ejection time ratio	73 %%	93 %	87 %	85 %	Schenone et al.
	90.9 %	77.1 %	95.4 %	52.7 %	Büke et al.
Fetal Tibia epiphysis	95.5 %	91.7 %	73.3 %	98.8 %	Abdulla et al.
Fetal femur epiphysis	97.7 %	50.0 %	75.0 %	93.5 %	Abdulla et al.
Thalamic echogenicity	77.3 %	75.0 %	31.0 %	85.8 %	Abdulla et al.
Amniotic fluid vernix	63.6 %	66.7 %	20.0 %	93.3 %	Abdulla et al.
Biparietal diameter	56.8 %	83.3 %	20.8 %	96.2 %	Abdulla et al.
Placental grading	60.2 %	75.0 %	20.5 %	94.6 %	Abdulla et al.
QuantusTLM	74.3 %	88.6 %	95.5 %	51 %	Palacio et al. [50]

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