Amniocentesis for Fetal Lung Maturity: Will It Become Obsolete?

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Amniocentesis for fetal lung maturity has historically been performed for many reasons: uterine and placental complications, maternal comorbidities, fetal issues, and even obstetric problems. Even though the risks associated with third trimester amniocentesis are extremely low, complications have been documented, including preterm labor, placental abruptions, intrauterine rupture, maternal sepsis, fetal heart rate abnormalities, and fetal-maternal hemorrhage. This review presents the types of tests for fetal lung maturity, presents the indications and tests utilized, and discusses recommendations for when amniocentesis for fetal lung maturity may be appropriate.

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KEY WORDS

Fetal lung maturity • Amniocentesis • Lecithin/sphingomyelin ratio • Respiratory distress syndrome

Management of complicated high-risk pregnancies continues to evolve. Since the discovery of ultrasound and antenatal fetal testing, increasing emphasis has been placed on optimizing fetal outcomes. With the discovery of the lecithin/sphingomyelin (L/S) ratio by Gluck and colleagues,[1] amniocentesis and assessment of fetal lung maturity began to be included in some algorithms for management of these complicated pregnancies.

Recently, authorities have questioned the efficacy of assessing fetal lung maturity.[2] This issue leads us to question whether fetal lung maturity obtained at the time of amniocentesis should continue to be a part of modern obstetric management. The advantage of this procedure is that it can help prevent respiratory distress syndrome (RDS) if fetal lung maturity testing is positive. The disadvantages include its lack of 100% accuracy and its inability to predict or prevent many other complications these neonates can develop.[3]

This review presents the types of tests for fetal lung maturity, presents the indications and tests utilized, and discusses the complications of the procedures. We discuss the controversy surrounding the use of tests for fetal lung maturity that has recently been raised. Our goal as obstetricians should be to optimize the outcomes of both the mother and the fetus.

Types of Tests for Fetal Lung Maturity

In an attempt to determine if fetal lung maturation has occurred to a point sufficient to avoid the development of fetal RDS, numerous tests have been developed. The different tests are based on the following four basic themes: biochemical testing for active components of surfactant, biophysical testing for functionality of surfactant, physical testing of the opacity of amniotic fluid, and ultrasound evaluation of the fetus and its tissues (Table 1).

TABLE 1

Types of Tests Used for Evaluation of Fetal Lung Maturity

Biochemical Testing for Active Components of Surfactant
- Lecithin/sphingomyelin ratio
- Phosphatidylglycerol
- Surfactant/albumin ratio
- Lung profile
- Lecithin/sphingomyelin ratio and percentages of phosphatidylglycerol, desaturated lecithin, and phosphatidylinositol
- Saturated phosphatidylcholine

Biophysical Testing for Functionality of Surfactant
- Shake test
- Foam stability index
- Tap test

Physical Testing of the Opacity of Amniotic Fluid
- Looking at turbidity
- Optical density at 650 nm
- Lamellar body counts
- Nile blue hydrochloride staining

Ultrasound evaluation of the fetus and its tissues
- Biparietal diameter
- Placental grade
- Coefficient of variation of the grey levels of placentas, fetal lungs, and livers
- Pulmonary artery Doppler

The L/S ratio was first described by Gluck and colleagues in 1971.[1] This test is undertaken by using thin-layer chromatography, and is technique dependent.[4] The test takes advantage of the constant levels of sphingomyelin in the third trimester of pregnancy, as lecithin levels increase with a maturing lung. An L/S ratio of 2.0 is usually considered an indication of maturity. Limitations of this test are that blood and meconium interfere with the results,[5,6] it is difficult to perform, and the test is time consuming. A sample will remain stable for 24 hours at room temperature, but can be stored for 12 months at −20°C.[7]

Phosphatidylglycerol (PG) usually appears late in gestation, several weeks after the L/S ratio. Initially, testing for PG was also done with thin-layer chromatography, but the development of a rapid slide agglutination test simplified matters.[8] This test has been marketed as the AmnioStat-FLM® (Irvine Scientific, Santa Ana, CA).[9] This test can also be used in samples recovered from vaginal pools, as well as those with blood or meconium.[10]

The surfactant/albumin ratio looks at competitive binding of a florescent albumin probe and surfactant in amniotic fluid using polarized light. The level of polarization is lower as more surfactant is present. This was initially described by Shinitzky and associates in 1976.[11] In the 1980s, Tait and associates[12] and Russell[13] each used the Abbott TDx (Abbott Laboratories, Abbott Park, IL) platform to standardize the test with widely available equipment. Russell used PC-16 dye and his version was marketed as the TDx FLM. It was later modified in 1995 and marketed as the TDx FLM II. This test is currently not available commercially.

Other tests have been described. Kulovich and colleagues[14] described using a lung profile looking at L/S ratio, the percentages of PG, dissaturated lecithin, and phosphatidylinositol. Saturated phosphatidylcholine uses thin layer chromatography and is valid with blood and meconium.[15] Surfactant associated with phospholipid membranes can be measured by incubating a lipid soluble dye with amniotic fluid for 20 minutes and looking at fluorescent polarization with a microviscometer, as long as blood and meconium are absent.[16,17]

Biophysical Testing for Functionality of Surfactant

The shake test was initially described by Clements and associates in 1972.[18] In the initial report, amniotic fluid and an equal volume

of 95% ethanol were shaken, and a ring of bubbles was looked for at the meniscus. The following year, Edwards and Baillie[19] used 100% ethanol, resulting in a final ethanol volume of 47.5% to 50%.

The foam stability index is a semiquantitative version of the shake test.[20] This test takes various volumes of 95% ethanol added to 0.5 mL of centrifuged amniotic fluid (1000 g for 3 min), giving a final ethanol volume of 42% to 55%. The tubes are shaken for 30 seconds and allowed to rest for 15 seconds. A stable ring of bubbles at over 48% ethanol volume is considered mature. This test was marketed as the Lumadex-Foam Stability Index Test (Beckman Instruments, Brea, CA).[21] The commercial test was discontinued in 1997. Blood and meconium are associated with false mature results.

The tap test involves the breakdown of bubbles in an earlier layer. This test involves adding 1 mL of amniotic fluid to 1 drop of 6N hydrochloric acid and 1.5 mL of diethyl ether. After tapping four times, a mature test has no bubbles left in the ether layer at 2 minutes.[22,23]

Physical Testing of the Opacity of Amniotic Fluid

Simply looking at the turbidity of amniotic fluid has been studied. Sbarra and associates[24] published an article regarding untrained observers who were able to correctly identify mature versus immature unspun amniotic fluid samples. Strong and colleagues[25] looked at the ability to read newsprint through a sample of amniotic fluid, showing that if unreadable, 97% were mature.

The optical density of amniotic fluid at 650 mm has also been studied. In a study by Turner and Read,[26] the optical density at 650 nm (OD650) was found to be superior to the L/S ratio for predicting which premature newborns would have mature lungs. Another study by Sbarra and colleagues[27] showed that if the OD650 was $\geq$ 0.15 the L/S ratio was always $>$ 2.0. This test may be used with blood present, but not with meconium.

Lamellar body count (LBC) is a simple, rapid test for determining fetal lung maturity. Type II pneumocytes store surfactant in lamellar bodies, which are then secreted into the alveolar spaces. These structures are similar in size to platelets, allowing for automated counting by hematologic counters. In 2001, Neerhof and associates[28] published a consensus on protocol with counts $>$ 50,000/μL as mature and $<$ 15,000/μL as immature. It should be noted, however, that despite the consensus paper, different analyzers use different methods for counting platelets, and specific cutoffs need to be developed for each analyzer.[29] Meconium has been noted to raise the count by 5000/uL, whereas blood (hematocrit $>$ 1%) will initially raise the count, but then lower the count as clotting traps the lamellar bodies like platelets.[30] Morrison and colleagues[31] looked at Nile blue hydrochloride staining and found that if $>$ 10% of cells were stained, none of the newborns developed RDS.

Ultrasound Evaluation of the Fetus and Its Tissues

Campbell[32] used the biparietal diameter in 1969 as an early attempt to predict lung maturity based on ultrasound measurements. In 1986, Shah and Graham[33] looked at placental grade and found that fetuses with grade 3 placentas (N = 43) had no cases of RDS. Expanding on the tissues examined, Podobnik and colleagues[34] looked at the coefficient of variation of the grey levels of placentas, fetal lungs, and fetal livers, as predictors of pulmonary maturity. Recently, fetal pulmonary artery Doppler has been used to predict neonatal RDS. Kim and coworkers[35] found that an elevated acceleration-to-ejection time ratio was significantly associated with neonatal RDS. Table 1 reviews the available tests for determining fetal lung maturity.

Accuracy of the Tests

All of the tests used to evaluate fetal lung maturity by amniocentesis have been shown to have good sensitivity (proportion of immature tests results in neonates with RDS) and negative predictive values (probability of no corresponding RDS with a mature fetal lung maturity test result).[36] However, they all have a low positive predictive value (probability of RDS with an immature fetal lung maturity test result). The TDx FLM II was shown by Fantz and colleagues[37] to have 100% sensitivity with a result of 45 mg/g, but neonates born without RDS with results as low as 14.6 mg/g. L/S ratios $\geq$ 2 have been shown to have a low incidence of RDS.[1] In a review, Grenache and Gronowski[38] found negative predictive values ranging from 86% to 100%. However, Creasy and Simon[39] noted this finding was related to gestational age and that an L/S ratio $<$ 2 was only slightly better than an accurate assessment of gestational age at predicting hyaline membrane disease. A positive PG test result may be better than an L/S ratio at predicting fetal lung

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maturity. According to Hallman and Teramo,[40] the false-positive result rate for an L/S ratio is 5%. However, the absence of PG does not predict RDS.

Grenache and Gronowski[38] found LBC to be equal to or better than L/S ratio. In their review, 7 of the 10 studies had sensitivities of 100%, but specificities ranged from 54% to 100%. They also suggested that analyzer-specific cutoffs are required, and should be confirmed with outcome-based studies by each laboratory offering the test. The foam stability index also has excellent sensitivities of 98% to 100%, but its specificities are approximately 85%.[36,41,42] There are currently no commercial tests available for foam stability.

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The aforementioned tests have another problem in common, which is the fact that they have used a single cutoff value regardless of gestational age to determine fetal lung maturity. Almost 30 years ago, Creasy and Simon[43] found after 34 weeks, and especially after 37 weeks, that an L/S ratio < 2 was only slightly better than an accurate assessment of gestational age at predicting hyaline membrane disease. McElrath and colleagues[44] showed that using the TDx/TDxFLx Fetal Lung Maturity II surfactant-to-albumin assay, the predicted risk of neonatal RDS not only depended on the assay value but also on the gestational age and assay value. For example, an infant with a TDx-FLM II of 50 mg/g at 28 weeks had a 25% chance of RDS, whereas an infant at 34 weeks with the same test value had only a 6% chance of RDS. Parvin and associates[45] confirmed this relationship 1 year later. Karcher and coworkers[46] not only found similar results with the surfactant-to-albumin ratio, but with the LBC as well.

Historical Indications for Amniocentesis

Historically, amniocentesis has been used to evaluate fetal lung maturity for a variety of medical and obstetric indicators with the plan to deliver the mother if fetal lung maturity is documented. All of the indications that have been reported in the literature are presented in Table 2. Table 3 summarizes all of the data on fetal lung maturity published to date.

Interestingly, what one center uses as indicators for an amniocentesis, others do not. This lack of consistency suggests that as obstetricians became more comfortable with the procedure more assessments were performed, thus expanding the indications for the procedure. This expansion of indications could explain the increase in late preterm deliveries we see in the United States, because centers are performing amniocentesis on patients early and delivering the patients if maturity is documented.

Indications

The preponderance of evidence reported in the literature over the past several years indicates that neonatal morbidity is increased, regardless of a positive fetal lung maturity test result in infants born prior to 39 weeks of gestation. With regard to nonelective deliveries, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Bethesda, MD) and the Society of Maternal Fetal Medicine (Washington, DC) held a workshop in February 2011, titled *Timing of Indicated Late Preterm and Early Term Birth*. The consensus and findings were published in August 2011.[2] This publication clearly states that if a delivery is indicated, the results of a fetal lung maturity test should not alter the decision to deliver. Conversely, if delivery could be postponed in the event of an immature test result, the patient lacks a sufficient indication for delivery in the first place.

Based on this consensus, the indications for amniocentesis to determine fetal lung maturity have been significantly narrowed. In fact, one

TABLE 2

Historic Indications for Amniocentesis for Fetal Lung Maturity

1. Diabetes
2. Chronic hypertension
3. Cholestasis
4. Fetal anomalies
5. Intrauterine growth restriction
6. History of preterm delivery
7. History of uterine surgery
8. Oligohydramnios
9. Multiple gestations
10. Polyhydramnios
11. Poor dating
12. Post maturity
13. Preeclampsia
14. Placenta previa
15. Preterm labor
16. Preterm premature rupture of the membranes
17. Rule out intrauterine infection
18. Rh disease
19. Vaginal bleeding
20. Maternal complications
21. Macrosomia
22. Fetal heart rate abnormalities
23. Elective deliveries
24. Other

TABLE 3

Indications, Literature Citations, and Number of Patients Per Study for Evaluation of Amniocentesis for Fetal Lung Maturity

	Jan. 1977	June 1978	Oct. 1981	Sept. 1982	May 1986	Oct. 1993	Oct. 1995	1996	Oct. 1997	Feb. 2002	May 2003	2005	Nov. 2005	April 2006	Jan. 2008	May 2009	July 2010	July 2010	July 2010	Dec. 2010	June 2011	Total
	Morrison JC et al[31]	Young BK[57]	Klein SA et al[58]	Chervenak and Shamsi[59]	Garite TJ et al[60]	Whigton TR et al[61]	Rodriguez-Macias KA[62]	Piazze JJ et al[63]	Bonebrake RG et al[64]	Gordon MC et al[65]	Kesselman EJ et al[66]	Piazze JJ et al[63]	Bildirici I et al[67]	Hodor JG et al[73]	Stark CM et al[55]	Janicki MB et al[69]	Azpurua H et al[68]	Shanks A et al[70]	Wijnberger LD et al[71]	Bates E et al[3]	Kamath BD et al[72]	
Cholestasis, liver disease		3						3				7		6						13		29
CHTN	76		5			20	38	28				45		10						33	33	288
DM	72	88	27			9		11			14	13		89	47	120				170	40	612
Elective				1	79				48	285	36					26	8			19	103	605
Fetal anomaly															10							10
Fetal jeopardy					12				7							3						22
FGR			5				7	25		62	1	32	5	9					66		9	155
h/o PTD																					57	57
h/o Uterine surgery	508	102	64						31				30		11	18	10	7		105	68	852
Induction of labor	26																					26
Macrosomia													2			12						14
Maternal complication	48	6			20						17		20			9			49			114
Multiples								16			5	32			4							57
Normal								69				74										143
Oligohydramnios								3				20									14	37
Other	32	5	1	2	5	29		19	2	52		53	2	24				3	111	63	15	302
Polyhydramnios				1				4														5
Poor dating	31			7											21							59
Poor OB history	58		3	1													2			13		77
Postmaturity	58	15	14																			72
Preeclampsia/PIH	106	48	17								2		2		3					24		154
Placenta previa						16	3				19		10	11	5	19	7		17	19		109
PTL/PPROM	31					146	18	13	20	163	31	25	12	18		1			17		95	573
R/O infection		2						5				5			9							19
Rh disease	29	14	7	1			4				2											43
Threatened PTD					56																	56

CHTN, chronic hypertension; DM, diabetes mellitus; FGR, fetal growth restriction; h/o, history of; OB, obstetric; PIH, pregnancy-induced hypertension; PPROM, preterm, premature rupture of membranes; PTD, preterm delivery; PTL, preterm labor; Rh, Rhesus; R/O, rule out.

could argue that the only remaining indications are restricted to those patients in whom accurate fetal dating is absent. The American Congress of Obstetricians and Gynecologists (ACOG) considers one of the following criteria to be necessary in order to consider a pregnancy to be at term: (1) ultrasound measurement at < 20 weeks of gestation, (2) fetal heart tones documented as present for 30 weeks by Doppler ultrasonography, or (3) 36 elapsed weeks from the date of a positive serum or urine pregnancy test result.[47] It would seem reasonable to utilize amniocentesis for fetal lung maturity testing in patients with poor dating when elective repeat cesarean delivery is planned. In addition, in patients with poor dating and with indications for late preterm or early-term delivery, amniocentesis for fetal lung maturity may be of benefit in determining the timing of some deliveries (Table 2).

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Recommendations

Over the years, indications for amniocentesis for fetal lung maturity have changed. During most of this time, they have expanded. However, in light of recent data and the increasing use of biophysical profiles and Doppler ultrasound, this trend has been reversed.

One of the problems of using a mature biochemical test for fetal lung maturity as an indication for delivery is that such a test does not assure the absence of other morbidities, or, as discussed earlier, respiratory problems when delivering an infant before 39 weeks of gestation. Two studies have looked at composite risk for late preterm and early term infants as compared with infants born at 39 weeks. These composite indices, although slightly different, included admission to the neonatal intensive care unit, treated hypoglycemia and hyperbilirubinemia, presumed or confirmed sepsis, ischemia encephalopathy, periventricular leukomalacia, and death, as well as adverse respiratory outcomes. Bates and colleagues[3] found that infants born at 39 weeks had a 2.5% mortality and morbidity composite index, whereas infants born at 38 weeks had a 5.2% mortality and morbidity composite index.

The recommendation for amniocentesis with placental or uterine complications such as placenta previa, placenta accreta and its variants, previous classical cesarean delivery, or myomectomy has virtually disappeared. If there is an urgent fetal or maternal need for delivery, it should be performed. Otherwise, it is recommended that patients with placenta previa be delivered at 36 to 37 weeks,[48] and those with placenta accreta, increta, and percreta be delivered at 34 to 35 weeks.[49] Women with a previous classical section should be delivered at 36 to 37 weeks.[50-52] The recommendation for women with previous myomectomy, who require a cesarean delivery, is to deliver them at 37 to 38 weeks, unless they had a complicated or extensive surgery during their myomectomy.[2] In those cases, they may need to be delivered earlier.

Another major category that was used in the past as an indication for amniocentesis is fetal complications, including fetal growth restriction, fetal anomalies, and multiple gestations. It is now recommended that fetuses with uncomplicated fetal growth restriction be delivered at 38 to 39 weeks, as long as fetal well-being is assured.[2] If there are comorbidities or concurrent complications such as oligohydramnios, then delivery may need to occur as early as 34 weeks. With twin gestations, delivery should take place between 32 and 38 weeks, depending on the chorionicity, whether the twins are monoamniotic or diamniotic, and if other complications exist.[2] A fetus with congenital anomalies should usually be delivered between 34 and 39 weeks, depending on the anomaly itself, the potential for fetal or maternal complications, or concurrent maternal disease.[2] Of course, if at any time fetal well-being is not assured, then delivery may be considered before these recommendations.

Previously, maternal comorbidities or complications such as chronic hypertension, preeclampsia, and diabetes have been indications for amniocentesis for fetal lung maturity. Women with chronic hypertension, without superimposed preeclampsia and other maternal or fetal complications, should be delivered between 36 and 39 weeks, depending on whether they are on medication or not and if their blood pressures are controlled.[53] Patients with mild preeclampsia should be delivered at 37 weeks and those with gestational hypertension can be delivered at 37 to 38 weeks.[2] Patients with severe preeclampsia diagnosed at 34 weeks or later should be delivered at the time of diagnosis.[2] Those with well-controlled pregestational diabetes without evidence

of vascular disease and those with gestational diabetes who have well-controlled blood sugars, whether by diet control or medication, should not be delivered before 39 weeks. Those with pregestational diabetes who have vascular disease and well-controlled blood sugars may be delivered as early as 37 weeks.[2] Those with poorly controlled diabetes, whether pregestational or gestational, may need to be delivered as early as 34 weeks or as late as 39 weeks.[2] The management of these patients should be individualized. The above recommendations assume no other comorbidities and a reassuring fetal status.

The last major category that has been used as an indication for amniocentesis for fetal lung maturity involves obstetrical complications. Patients with preterm premature rupture of membranes (PPROM) at 34 weeks or later should be delivered at the time of diagnosis.[2,54] There may be a place for fetal lung maturity testing by amniocentesis or vaginal pooled amniotic fluid before 34 weeks. Mercer and colleagues performed a prospective randomized trial in patients with PPROM with documented fetal lung maturity between 32 and 36 weeks and randomized them to expectant management or immediate delivery.[74] The neonates in this group who had immediate delivery had a better outcome than the neonates who were expectantly managed. Suggesting knowledge of fetal lung maturity would be advantageous in patients with this complication. Patients in spontaneous preterm labor at 34 weeks or later should be delivered only if labor is progressive or there are other maternal or fetal indications for delivery. It is currently not recommended to deliver patients with a history of unexplained stillborn deliveries and without other complicating factors in the current pregnancy before 39 weeks. If late preterm or early term delivery before 39 weeks is considered, then amniocentesis for fetal lung maturity should be performed.

The last indication would be patients delivered for poor dating. An ACOG Bulletin recommends that prior to elective delivery in patients who do not meet the criteria of a well-dated pregnancy, fetal lung maturity be confirmed by an amniocentesis after 39 weeks by the best date the physician has.[47] This class of patients would include those electing repeat cesarean delivery who are not well dated.

Conclusions

Amniocentesis for fetal lung maturity has historically been performed for many reasons: uterine and placental complications, maternal comorbidities, fetal issues, and even obstetrical problems. Even though the risks associated with third trimester amniocentesis are extremely low, complications have been documented, including preterm labor, placental abruptions, intrauterine rupture, maternal sepsis, fetal heart rate abnormalities, and fetal-maternal hemorrhage.[55,56] Considering these rare occurrences, the lack of sensitivity and specificity of this testing, and the fact that other morbidities need to be considered (not just RDS), the indications for amniocentesis are indeed infrequent, except when dating does not meet ACOG standards for maturity. That said, there may be a place for amniocentesis when gestational age is not well documented. The statement by the joint workshop between the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Society for Maternal-Fetal Medicine conveys this proposition elegantly: "The rationale that if significant maternal or fetal risks exist, delivery should occur regardless of biochemical maturity and if delivery could be deferred owing to absence of pulmonary maturity there is not a stringent indication for prompt delivery."[2] Thus, amniocentesis for fetal lung maturity may become obsolete, except in patients with poor dating and where an elective delivery is desired. ■

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MAIN POINTS

- Amniocentesis to assess fetal lung maturity has historically been performed for many reasons, including uterine and placental complications, maternal comorbidities, fetal issues, and even obstetric problems. Recently, authorities have questioned the efficacy of calculating fetal lung maturity. This leads us to question whether fetal lung maturity obtained at the time of amniocentesis should continue to be a part of modern obstetric management.
- All of the tests used to evaluate fetal lung maturity by amniocentesis have been shown to have good sensitivity and negative predictive values; however, they all have a low positive predictive value.
- In patients with poor dating and with indications for late preterm or early-term delivery, amniocentesis for fetal lung maturity may be of benefit in determining the timing of some deliveries.
- If there is an urgent fetal or maternal need for delivery, proceed with amniocentesis.

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