Lamellar Body Count (Reference – 2013.02.002)
Notice of Assessment

December 2013
1 GENERAL INFORMATION

1.1 Requestor: CHUM

1.2 Application Submitted to MSSS: September 27, 2012

1.3 Application Received by INESSS: July 1, 2013

1.4 Notice Issued: October 31, 2013

Note
This notice is based on the scientific and commercial information (submitted by the requestor) and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE

2.1 Name of the Technology
Lamellar body count in amniotic fluid to assess fetal lung maturity. The count is obtained from a Coulter automated analyzer used in hematology for blood and platelet counts given the similar diameters of lamellar bodies (1–5 µm) and platelets (2–4 µm).

2.2 Brief Description of the Technology with Technical and Clinical Specifications
Structurally, lamellar bodies consist of concentric layers holding densely packed reserves of pulmonary surfactant [mainly phospholipids (90%), comprised of lecithin (L), sphingomyelin (S) and phosphatidylglycerol (PG), among other substances, and proteins (10%)] produced by the fetal lung [Lu et al., 2008].

Surfactant is produced by pneumocytes at 28 weeks’ gestation, and its concentration increases to term. At 34 weeks’ gestation or more, the quantity of surfactant is sufficient to prevent pulmonary atelectasis at birth and avert respiratory distress syndrome (RDS) in the neonate, a major cause of neonatal death among children born prematurely. In some high-risk pregnancies in which premature birth is a possibility, the prior determination of fetal lung maturity is essential to avoid RDS.

Various tests of fetal lung maturity have been proposed since 1971. In 1989, Dubin proposed the lamellar body count (Figure 1) using a hematologic cell counter, since lamellar body diameters are similar to those of platelets.

Two conditions are important: the condition of the amniotic fluid sample and the type of automated counter used. Amniotic fluid, preferably collected abdominally, must be free of blood, mucous and meconium and should not be centrifuged. Automated counters use various reading techniques: optical analysis of light refraction by laser beam (e.g., Bayer ADVIA analyzer, now manufactured by Siemens), electrical or radiofrequency impedance (e.g., Siemens Sysmex analyzer and Beckman Coulter analyzer) or even a combination of the two techniques (e.g., Abbott Laboratories Cell-Dyn analyzer), thus producing different results [Lu et al., 2008]. The reference device suggested by the requestor is the Coulter LH 750, for which a standardization consensus has been established by several authors [Neerhof et al., 2001a; Lockwood et al., 2010].
Figure 1: Electron Microscopy Photomicrographs of Lamellar Bodies (× 40,000)


2.3 Company or Developer
Not applicable. Amniotic fluid samples will be analyzed by means of an automated counter used for complete blood count analysis.

2.4 Licence: Not applicable.

2.5 Patent: Not applicable.

2.6 Approval Status (Health Canada, FDA): Not applicable.

2.7 Weighted Value: 5.40.

3 CLINICAL INDICATIONS, PRACTICE SETTING AND TESTING PROCEDURE

3.1 Targeted Patients
Fetuses, mainly before 34 weeks of gestation, when premature birth is anticipated, either spontaneously in the case of preterm labour with or without rupture of membranes, or medically indicated because of a risk of fetal or maternal complication.

3.2 Targeted Disease
At the time of preterm birth (< 37 weeks), but especially prior to fetal lung maturity (generally at 34 weeks), neonatal lungs cannot achieve normal expansion because of a lack of surfactant, produced mainly by Type II fetal pneumocytes. Consequently, neonatal respiratory distress syndrome (RDS) can develop, necessitating neonatal intensive care with mechanical ventilation. RDS affects 1% of all live births and 10% of all preterm infants [Besnard et al., 2013]. RDS of the neonate is a major cause of mortality among preterm infants and is associated with significant morbidity (including pulmonary fibrodysplasia, apnea and retro-lenticular blindness) among survivors.
Knowing the state of fetal lung maturity or immaturity before birth will permit, in the event of pulmonary immaturity, reassessing the indication for pre-term delivery or lowering the risk of neonatal RDS by maternal antenatal glucocorticoid therapy (certainly not without possible adverse effects) 24 to 48 hours prior to delivery, which could reduce the risk of RDS by at least 25%, or by instillation of exogenous surfactant into the neonate’s airways at delivery.

3.3 Number of Patients Targeted

The preterm birth rate of about 8% in Quebec per 85,000 births represents nearly 7,000 children born before 37 weeks. Fewer than 10% of these are born before 32 weeks and are at high risk of developing RDS, and about 10% to 15% are born between 32 and 34 weeks, with a mild to moderate risk of RDS. Thus, about 1,300 to 1,500 children are at risk per year.

The vast majority of women at risk of spontaneous pre-term labour before 34 weeks are given glucocorticoid therapy immediately. It is therefore only in ambiguous cases involving uncertain gestational age or of serious maternal or fetal complications (such as uncontrolled diabetes [which is known to delay fetal lung maturity], renal or severe hypertensive disease, or nonreassuring fetal status) that an amniocentesis for assessing fetal lung maturity will be performed. It is therefore expected that the test will be done a few hundred times each year in Quebec.

3.4 Medical Specialties Involved

Concerning preterm labour for medical indication: obstetrician-gynecologists, including fetal-maternal medical specialists at major perinatal clinics. Expertise in biochemistry/hematology is necessary to ensure sample quality and quality control of the measurement or automated counter.

3.5 Testing Procedure

Amniotic fluid should preferably be sampled by abdominal amniocentesis under direct ultrasound visualization. It must be free of mucous, blood and meconium [Lu et al., 2008].

Amniotic fluid should not be centrifuged (Grenache and Gronowski, 2006). Centrifugation reduces the number of lamellar bodies by one-third [Neerhof et al., 2001a; Lu et al., 2008]. Fluid is stable up to 10 days at room temperature and up to 50 days if refrigerated at 4°C [Lu et al., 2008]. Freezing is not recommended; in some instances, this decreases the count by 15% to 33% [Lu et al., 2008; Lockwood et al., 2010], while in others, the count remains unchanged [Grenache and Gronowski, 2006].

Once sampled, the amniotic fluid, lightly mixed for homogeneity of lamellar bodies, can be measured directly in a Coulter automated analyzer. Depending on the automated analyzer, the counting methods used are electrical impedance or light refraction to determine the dimensions of the particle and to distinguish it from other cellular components. The lamellar bodies from the amniotic fluid are quantified on the same detection channel as platelets owing to their similar size.

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology

According to the information provided by the requestor, this test replaces quantification of phosphatidylglycerol (PG) by thin-layer chromatography or by a slide immune adherence hemagglutination test with a commercial polyclonal antibody.
4.2 Brief Description of the Current Technological Context

There are two types of tests to measure fetal lung maturity: biochemical and biophysical. Biochemical tests measure the concentration of particular components of fetal lung surfactant, especially the phospholipids, whereas biophysical tests evaluate the effects of these phospholipids. The latter tests are not widely used: one measures optical density at 650 nm and the other is based on the foaming property of surfactant in the presence of anhydrous ethanol (semi-quantitative test proposed by Clements et al. in 1972), also called the shake test or the Foam Stability Index.

The first biochemical test was based on the rapid increase, with gestational age, of lecithin (L or phosphatidylcholine) relative to sphingomyelin (S), establishing fetal lung maturity when the L/S ratio is > 2.0 or 2.5 [Gluck et al., 1971]. This test is performed using thin-layer chromatography, a technique requiring special skills and thus not available at all times. It is a relatively expensive technique, requiring several hours to complete; it has good sensitivity, but lacks specificity in addition to having a poor inter-laboratory analytic precision.

Another test, considered by many to be the gold standard, involves measuring a phospholipid secreted very late (around 35 weeks) by the fetal lung: phosphatidylglycerol (PG), measured by thin-layer chromatography [Hallman et al., 1976]. This test has the same drawbacks as the L/S ratio. One kit, the Amniostat-FLM assay (Irvine Scientific, Ca, USA), has the ability to detect the presence of PG in amniotic fluid within 30 minutes using an enzyme immunoassay with an anti-PG polyclonal antibody [Lockitch et al., 1984; Eisenbrey et al., 1989]. This rapid test could be used if the sample contained blood or meconium, but it shared the same drawback of the late appearance of PG, with 50% positivity at 34 weeks, a critical period for delivery in certain high-risk pregnancies.

The test most commonly used in North America measured the surfactant-to-albumin ratio by fluorescence polarization, based on the principle of competitive binding of a fluorescent probe to albumin and fetal pulmonary surfactant in amniotic fluid. The method, first developed by Shinitzky et al. [1976] was later improved [Russell, 1987] and modified in 1995 to be offered as a commercial kit (TDX-FLM II; Abbott Laboratories, IL, USA). This test, with 100% sensitivity and 84% specificity, was recommended in 1999 by the National Academy of Clinical Biochemistry in the United States because of its clinical validity, analytical precision, round-the-clock availability, and 90-minute turnaround time for results. However, the commercial suppliers indicated that the kit would be discontinued in 2011, thus commanding a search for an option presenting the same clinical and technical characteristics.

Lamellar body count, first proposed by Dubin in 1989, is an attractive alternative.

4.3 Brief Description of the Advantages Cited for the New Technology

Lamellar body count uses standard equipment available in all institutions that perform simple hematological analyzes such as blood and platelet counts. The technique is automated and does not require expert handling. The technique can be performed in 30 minutes, from sample collection at the bedside (amniocentesis) to results. The measurement itself takes less than five minutes. The technique is available at all times and is not expensive. Lastly, the technique is more sensitive and precise than the other methods (see Analytical Validity).

However, some precautions should be taken with the amniotic fluid. Abdominal amniocentesis is preferred to avoid the presence of mucous, which increases the lamellar body count [Lockwood et al., 2010]. The presence of blood decreases the concentration, while the presence of meconium increases it [Lockwood et al., 2010]. Proper sample handling is important: the content of the tube is lightly mixed, but it must not be frozen (reduces the concentration) [Lockwood et al., 2010]. Lastly, the type of automated analyzer used affects the count [Kyle and Lawrence, 2012; Lockwood et al., 2010; Janicki et
al., 2009; Szallasi et al., 2003]. Accordingly, each laboratory should establish its own standards depending on the type of analyzer available at its institution. Information is still lacking on inter-laboratory quality control.

4.4 Cost of Technology: Not assessed.

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced

According to the requestor, this test would replace measurement of PG, which has the drawback of appearing very late (after 35 weeks) with 50% positivity at 34 weeks and therefore a low positive predictive value. In addition, the latter test, based on thin-layer chromatography, requires special technical skill, is costly and time-consuming. A lamellar body count is available round the clock, is very quick (< 30 minutes), inexpensive and more precise.

5.1.2 Diagnostic Value

The determination of fetal lung maturity by means of a lamellar body count can predict maturity, transitional maturity (uncertain) or immaturity based on the number (in tens of thousands) of lamellar bodies per microlitre of amniotic fluid.

Fetal lung maturity is confirmed by the absence of RDS at neonate delivery and during the first hours of life. Accordingly, one can determine the diagnostic accuracy of an insufficient lamellar body count (below a consensus cut-off) for predicting RDS.

Fetal Lung Maturity Cut-offs

Much discussion has surrounded the lamellar body count cut-off value in amniotic fluid at which fetal lung maturity can be established. Since 2001 [Neerhof et al., 2001a], several groups have proposed boundary values for determining whether a fetal lung is mature [Kyle and Lawrence, 2012; Tsuda et al., 2011; Janicki et al., 2009; Sapa et al., 2009; Lu et al., 2008; Grenache and Gorowski, 2006; Szallasi et al., 2003].

Most authors agree on establishing fetal lung maturity at 50,000 particles/microlitre (µL) of amniotic fluid, intermediate maturity (transitional maturity) between 15,000/µL and 49,000/µL, and immaturity at < 15,000/µL, when the count is performed with a Coulter LH 750 analyzer [Lockwood et al., 2010; Neerhof et al., 2001a].

The variations among the various auto-analyzers have been documented in several publications [Kyle and Lawrence, 2012; Janicki et al., 2009; Lu et al., 2008; Szallasi et al., 2003]. Depending on the selected cut-off value, their sensitivity is similar, but with a greater variability in specificity [Janicki et al., 2009; Lu et al., 2008; Szallasi et al., 2003].

It should be noted that Zhao et al. [2013] recently proposed a table of absolute risks for developing RDS based on lamellar body count and gestational age between 32 and 39 weeks. The calculation is based on an 8.5% prevalence of RDS in the population, but Zhao et al. propose a formula for reassessing the risk based on the local prevalence of the laboratory performing the test.

5.1.3 Therapeutic Value (In Terms of Therapeutic Choice Associated With Test Result)

In the event of immaturity, glucocorticoids can be administered to the mother 24 to 48 hours before delivery, or surfactant can be instilled in the neonate’s airways at birth.
5.2 Clinical Validity

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Two meta-analyses bring together more than twenty publications on the topic of clinical validity. Wijnberger et al. [2001] analyze 6 studies published between 1991 and 1996, while Besnard et al. [2013] analyze 13 studies published between 1999 and 2006, in which lamellar body count techniques and the L/S ratio technique are compared for evaluating fetal lung maturity and for their performance in predicting RDS. As regards the L/S ratio, the technique was relatively similar among all publications, whereas the lamellar body count techniques presented considerable heterogeneity depending on the preparation of the amniotic fluid, whether or not it was centrifuged, the type of auto-analyzer, and the reference threshold used.

The first meta-analysis reports sensitivity and specificity between 64% and 92% and between 81% and 100%, respectively, for the L/S ratio, compared with 71% to 100% and 73% to 100%, respectively, for the lamellar body count. Comparison of the two ROC curves indicates a seemingly better predictive performance of the lamellar body count versus the L/S ratio, but the difference is not statistically significant [Wijnberger et al., 2001].

Bensard et al. [2013] report the results of a dozen studies in which a lamellar body count was performed for over 2,400 patients. With a prevalence of RDS ranging from 6% to 32%, depending on the study, the sensitivity and specificity for the L/S ratio ranged from 62% to 100%, and 64% to 89%, respectively. For the lamellar body count, the sensitivity and specificity ranged from 73% to 99%, and 60% to 100%, respectively. The subgroup analyses showed that a lamellar body count of 50,000 to 55,000 permits a very high sensitivity (0.99; 95% CI: 0.92-1.00) and 65% specificity, whereas a count from 15,000 to 25,000 is correlated with a very high specificity approaching 1. Here, too, the ROC curve of the lamellar body count is slightly higher than the ROC curve for the L/S ratio [Bensard et al., 2013].

Predictive values vary depending on the prevalence reported in the various studies. For example, Grenache and Gorowski [2006] review ten studies with prevalence of RDS ranging from 7.0% to 15.9%; they report positive predictive values ranging from 24% to 100%, and negative predictive values of 98% for 2 studies and 100% for the other 8.

Impact of Special Conditions

A lamellar body count can be affected by certain specimen collection conditions or by maternal or fetal clinical situations.

a. Vaginal Collection

Collection of amniotic fluid should preferably be done by abdominal amniocentesis. Vaginal collection of amniotic fluid at the time of spontaneous rupture of the membranes is associated with a significantly
decreased predictive performance. With a prevalence of RDS from 25% to 34%, predictive performance between vaginal collection and abdominal amniocentesis is 38.4% versus 60.9% for sensitivity, 69.6% versus 89.9% for specificity, and 0.52 ± 0.08 versus 0.84 ± 0.03, respectively, for the area under the ROC curve [Wijnberger et al., 2010].

b. Twin Pregnancy
The predictive performance of the lamellar body count is not altered in the case of a twin pregnancy. In a series of 302 twin pregnancies between 29 and 38 weeks, reported by Tsuda et al. [2012], the predictive performance (in terms of sensitivity, specificity and area under the ROC curve) was similar to that for singleton pregnancies. With a count of 29,500/µL of amniotic fluid, sensitivity was 91.5% versus 94.0%, specificity was 83.3% versus 82.4% and the area under the ROC curves, 96.1% and 92.7% for twin pregnancies and singleton pregnancies, respectively [Tsuda et al., 2013; 2010].

c. Intrauterine Infection
Based on 365 amniotic fluid samples, 13 of 42 pregnancies before 34 weeks of pregnancy (28 to 33 weeks) presented an intrauterine amniotic infection, as determined by a glucose concentration in the amniotic fluid of < 0.8 mmol/L and a CRP of > 0.3 mg/dL. No neonate developed RDS. The lamellar body count was greater than 50,000/µL, except in two cases (22,000 and 34,000/µL). This count was significantly higher than the cut-off value of the pregnancies without intra-amniotic infection (p < 0.05) [Tsuda et al., 2010].

d. Maternal Diabetes
Maternal diabetes is associated with delayed fetal lung maturity. However, the presence or absence of maternal diabetes does not show a significant difference between 34 and 38 weeks; the lamellar body count was 145,000/µL among 14 diabetic mothers versus 116,000/µL among 309 non-diabetic mothers. Before 34 weeks’ gestation, these values were lower but still similar: 18,000/µL among 3 diabetic mothers and 84,000/µL among 39 non-diabetic mothers [Tsuda et al., 2010]. The same is true for glycemic control, defined by a glycemic mean during the third trimester of < 6.7 mmol/L; among 187 women, the lamellar body count remained unchanged, whether glycemic control was adequate or not (De Luca et al., 2009).

e. Pregnancy-induced Hypertension, Growth Restriction
The impact of pregnancy-induced hypertensive disorders has been reported. Stimac et al. [2012] present a set of 25 cases of pre-eclampsia (PE), 74 cases of intrauterine growth restriction (IUGR), 63 cases of PE + IUGR, and 144 normotensive pregnancies without IUGR, over four gestational age periods. From 26 to 30 weeks and from 37 to 39 weeks, there is no difference among the groups. From 31 to 33 weeks, the PE cases have the same count as normotensive cases (80,000/µL), whereas the IUGR cases with or without PE have almost twice the count at 150,000/µL and 175,000/µL, respectively (p < 0.02 and p < 0.03). From 34 to 36 weeks, it is the PE cases which have significantly lower counts relative to the normotensive cases (145,000/µL versus 350,000/µL, p < 0.05), while all groups showed they had reached the fetal lung maturity cut-off [Stimac et al., 2012].

Another cohort of 72 hypertensive pregnancies [Torrance et al., 2008] did not show a significant difference in the number of lamellar bodies although the HELLP syndrome16 seems to be associated with a clinically significant reduction, but not statistically significant compared with normotensive cases (80,000/µL versus 15,000/µL, p = 0.053).

In short, the test’s clinical validity is supported in the obstetric clinical conditions reported.

5.3 Analytical Validity

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<td>Correlation between test and comparator</td>
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<td>Other, according to test type</td>
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Repeatability of the lamellar body count is excellent. Using a Coulter LH 750 auto-analyzer, Lockwood et al. [2010] report a very low coefficient of variation when the count in 3 amniotic fluid samples was determined 11 times within the same test (intra-assay variation), i.e., 1.8% for a count of 25,300/µL, 2.5% for 33,100/µL and 2.1% for 53,600/µL. This low variation was superior to that of two other types of auto-analyzers (Sysmex XE-2100 and Coulter Ac-T diff2). Repeated measurement on 6 different days of 4 amniotic fluid samples showed coefficients of variation of 5.1% for a count of 14,800/µL, 4.8% for 28,700/µL, 3.4% for 54,700/µL, and 1.9% for 66,000/µL. Here too, the coefficients of variation were better with the Coulter LH 750 auto-analyzer than with the Sysmex [Lockwood et al., 2010].

According to Sapa [2009], who tested 3 samples 10 times within the same test, the coefficients of variation ranged from 8.9%, with a count of 14,000/µL, to 2.9% for 76,600/µL, and to 2.2% for 156,000/µL.

Linearity, or the capacity to reproduce the expected result when the sample is diluted, was determined by producing final proportions of 100%, 75%, 50%, 25%, 10% and 5% of the initial concentration. Linearity with the Coulter LH 750 yielded an almost perfect global coefficient of correlation ($r^2 = 0.997$). It was the same with the Sysmex [Lockwood et al., 2010].

Stability of lamellar bodies was assessed at 4°C and -80°C. Lamellar bodies are stable for at least 33 days when refrigerated, with a variation of 1.2%, and up to 15.1% with the Sysmex auto-analyzer. A single freeze-thaw cycle caused a 31% mean decrease in the count, irrespective of the initial concentration of lamellar bodies. When the lamellar bodies were examined by electron microscopy, a denser arrangement of particles is observed, as well as a reduced size of the lamellar concentric structures [Lockwood et al., 2010].

The addition of whole blood to amniotic fluid has previously been reported to cause diphasic interference, with an initial increase followed by a decrease when the lamellar bodies form a fibrin aggregate [Lockwood et al., 2010], but this was not observed at a concentration of $0.03 \times 10^{12}$ red blood cells/L or less [Lockwood et al., 2010].

The addition of meconium artificially increases the count, which constitutes a contraindication of this test when the amniotic fluid contains meconium, as is reported by most authors.
5.4 Recommendations From Other Organizations

The US UpToDate review suggests the lamellar body count for first-line use [Gillen-Goldstein et al., 2013]; the Rex Pathology Laboratory Bulletin (North Carolina, US) makes the same recommendation [Benson, 2010].

6 ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources: Not assessed.

6.2 Economic Consequences: Not assessed.

6.3 Main Organizational Issues: Not assessed.

7 IN BRIEF

7.1 Clinical Relevance

The lamellar body count in amniotic fluid is used to assess fetal lung maturity in a preterm pregnancy. Test available round the clock, quick, easy and inexpensive.

7.2 Clinical Validity

Using a predetermined threshold value, a Coulter auto-analyzer and amniotic fluid sampled by abdominal amniocentesis and not centrifuged, test sensitivity and specificity range from 62% to 100% and 64% to 89%, respectively.

7.3 Analytical Validity

With standardization based on the Coulter auto-analyzer, within-test and between-test accuracy is excellent (often CV < 5%). Reproducibility and ability to reproduce the expected result with a sample at various dilutions are excellent ($r^2$ 0.997). In addition, the sample remains stable at room temperature and when refrigerated.

7.4 Recommendations From Other Organizations

This test is proposed for first-line use [Gillen-Goldstein et al., 2013], and would be the best option, given the 2011 discontinuation of a rapid kit-based test.
8  INESSS NOTICE IN BRIEF

Lamellar Body Count

Status of the Diagnostic Technology

- [x] Established
- [ ] Innovative
- [ ] Experimental (for research purposes only)
- [ ] Replacement for technology which becomes obsolete

INESSS Recommendation

- [x] Introduce test to Index
- [ ] Do not introduce test to Index
- [ ] Reassess test

Additional Recommendation

- [ ] Draw connection with listing of drugs, if companion test
- [ ] Production of an optimal use guide
- [ ] Production of indicators, when monitoring is required

Notes

The clinical indication for this test is clear.

However, a few points must be considered when introducing the test:

- The analytical precautions are significant (see text of Notice).
- Each laboratory must determine its threshold value.
- Interpretation of test results is difficult and requires expertise; a certain volume must be maintained for quality assurance.

It remains to be determined whether it is necessary to keep the phosphatidylglycerol assay (PG) or L/S ratio (code 30304) for assessing fetal lung maturity in cases where the lamellar body count is not possible for technical reasons (e.g., presence of meconium) or if it must be kept only at certain clinics.
REFERENCES


