The Changing Landscape of Fetal Lung Maturity Testing

David G. Grenache, PhD, DABCC
University of Utah
ARUP Laboratories
Salt Lake City, UT
Fetal Lung Development

http://www.embryology.ch/anglais/rrespiratory/phasen01.html
Pulmonary Surfactant

• Synthesized by type II pneumocytes and packaged into lamellar bodies

• Deposited at alveolar air-liquid interface and decreases surface tension of hydrated inner layer

• Inadequate concentrations may result in newborn respiratory distress syndrome
Respiratory Distress Syndrome (RDS)

- Caused by a deficiency in pulmonary surfactant
- Most common cause of respiratory failure in neonates
  - 8th leading cause of infant death (2007)
- Incidence is indirectly proportional to gestational age at delivery

<table>
<thead>
<tr>
<th>Weeks gestation at birth</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>60-80</td>
</tr>
<tr>
<td>32-36</td>
<td>15-30</td>
</tr>
<tr>
<td>&gt;37</td>
<td>5</td>
</tr>
<tr>
<td>Term</td>
<td>Rare</td>
</tr>
</tbody>
</table>

~20,000 newborns/year (US)
Fetal Lung Maturity (FLM) Tests

• Performed on amniotic fluid
  – 32-38^{6/7} weeks of gestation (ACOG 2008)

• Used for decision making
  – Allow or delay delivery w/ steroid administration
  – Uncertain gestational age
  – Transfer mother to facility with NICU

• Must have high sensitivity for immaturity & high negative (mature) predictive value

• Performed rapidly (ideally)
History of FLM Tests

- Lecithin/Sphingomyelin Ratio (1971)
- Phosphatidylglycerol (1983)
- Surfactant/Albumin Ratio (1986)
- Lamellar Body Count (1988)

• Marketed as Fetal Lung Maturity II by Abbott Laboratories
• Discontinued at end of 2011
• Reagent inventories to be exhausted in early 2012
Clinical Performance of FLM Tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV (mature)</th>
<th>PPV (immature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/A ratio</td>
<td>99%</td>
<td>71%</td>
<td>99%</td>
<td>28%</td>
</tr>
<tr>
<td>Lamellar body count</td>
<td>97%</td>
<td>71%</td>
<td>99%</td>
<td>43%</td>
</tr>
<tr>
<td>PG (AmnioStat FLM)</td>
<td>96%</td>
<td>70%</td>
<td>99%</td>
<td>29%</td>
</tr>
<tr>
<td>L/S ratio</td>
<td>84%</td>
<td>82%</td>
<td>96%</td>
<td>42%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| **L/S Ratio** | • Good sensitivity for immaturity  
• Quantitative  
• QC/PT available | • Technically difficult  
• Long analytical time  
• Imprecise  
• Effected by blood and meconium  
• Offered by few labs |
| **PG**   | • High sensitivity for immaturity  
• Unaffected by blood or meconium  
• Rapid  
• QC/PT available | • Late marker of pulmonary maturity  
• Qualitative test result  
• Subjective test interpretation  
• Single vendor |
| **LBC**  | • High sensitivity for immaturity  
• Rapid and quantitative  
• Instrumentation widely available  
• PT available | • Laboratory developed test  
• Effected by blood and meconium  
• Instrument-specific cutoffs for maturity  
• No commercial QC available |
Contemporary Issues
Decreasing Utilization of FLM Tests

Is the frequency with which you are ordering FLM tests increasing, decreasing, or staying the same?

Frequency

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreasing</td>
<td>20</td>
</tr>
<tr>
<td>No Change</td>
<td>60</td>
</tr>
<tr>
<td>Increasing</td>
<td>20</td>
</tr>
</tbody>
</table>

Why decreasing

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not necessary</td>
<td>80</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>10</td>
</tr>
<tr>
<td>Cost</td>
<td>5</td>
</tr>
<tr>
<td>Tests not available</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
</tbody>
</table>

Could you provide your current level of care without any FLM test results?

![Bar chart showing practice with and without FLM test results.](chart.png)

Which FLM test would you likely order if the S/A ratio were no longer available?

![Bar chart showing the percentage of selection for each test.]

Within how many hours do you require FLM test results?

<table>
<thead>
<tr>
<th>TAT</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>80</td>
</tr>
<tr>
<td>12-24</td>
<td>20</td>
</tr>
<tr>
<td>24-48</td>
<td>0</td>
</tr>
</tbody>
</table>

Timing of Elective Repeat Cesarean Delivery at Term and Neonatal Outcomes

- 13,258 C-sections
- Delivery before 39 weeks associated with adverse respiratory outcomes
- Elective delivery at <39 weeks discouraged unless fetal lungs are mature
Neonatal Outcomes After Demonstrated Fetal Lung Maturity Before 39 Weeks of Gestation

Elizabeth Bates, MD, Dwight J. Rouse, MD, MSPH, Merry Lynn Mann, BS, Victoria Chapman, MPH, Waldemar A. Carlo, MD, and Alan T. N. Tita, MD, PhD

(Obstet Gynecol 2010;116:1288–95)

- Two cohorts
  - 36-38 weeks with mature FLM test result (N=459)
  - 39-40 weeks (N=13,339)

- Delivery before 39 weeks associated with increased risk of adverse outcome

- Are FLM tests necessary anymore?
Summary

• RDS is caused by a deficiency of pulmonary surfactant and is inversely related to gestational age at delivery

• All currently available FLM tests are good to excellent predictors of lung maturity but not immaturity

• The overall frequency of FLM testing appears to be decreasing but tests are not likely to become obsolete

• The loss of the widely used S/A ratio means that many laboratories will need to offer a replacement FLM test

• The L/S ratio is an imprecise test with many disadvantages and should not be considered the gold standard test

• The LBC is a rapid FLM test and an excellent predictor of lung maturity but is a lab-developed test that requires thorough validation