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## Neonatal morbidity occurs despite pulmonary maturity prior to 39 weeks gestation

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### Abstract

**Objective**—To compare outcomes among late-preterm or early-term neonates according to fetal lung maturity status.

**Study Design**—We conducted a retrospective cohort study of 234 eligible singletons delivered after fetal lung maturity (FLM) testing prior to 39 weeks gestation at our center over a two year time period. A primary composite neonatal outcome included death and major morbidities.

**Results**—The overall rate of primary composite morbidity was 25/46 (52.2%) and 61/188 (32.4%) in the immature/transitional and mature groups, respectively. After adjustment for confounders including gestational age, the composite outcome was not significantly different; aOR 1.4 (CI 0.7-3.0). The rate of respiratory distress syndrome was significantly higher in the immature/transitional group; OR 3.4 (CI 1.1-10.3) as expected.

**Conclusions**—FLM status did not correlate with the spectrum of neonatal morbidities in late preterm and early term births. Neonatal complications remained common in both groups.

### Keywords

fetal lung maturity; late preterm birth; amniocentesis; neonatal outcomes; prematurity

### Introduction

Fetal lung maturation (FLM) studies often dictate obstetrical decision making in late preterm and early term pregnancies. In clinically appropriate circumstances, the status of FLM can provide an estimate of risk of neonatal respiratory distress syndrome and thus inform the timing of delivery.<sup>1</sup> However, recent evidence suggests that despite mature FLM testing,

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neonates born before 39 weeks gestation have more adverse outcomes than those born subsequent to 39 weeks.<sup>2-6</sup>

Although adverse respiratory outcomes are among the most common complications in the late preterm and early term populations, recent studies highlight the importance of neonatal maturation including outcomes not directly assessed by FLM testing.<sup>2-7</sup> Other common neonatal complications in the late preterm period include jaundice, feeding difficulties, temperature dysregulation, susceptibility to infection, and metabolic abnormalities. Notably, there is now a large body of evidence suggesting the late preterm period as a time for significant brain maturation. Cerebral cortex continues to develop anatomic complexity and to increase in volume throughout gestation. Half of cerebral cortex volume accumulates in the final 6 weeks of gestation.<sup>8-10</sup> Recent observations regarding the relationship between even subtle differences in gestational age with neonatal outcomes have led to reconsideration of criteria for timing delivery.<sup>2</sup>

While ample evidence shows that the risk of adverse outcomes differs between a neonate born prior to 39 weeks with mature FLM testing and a neonate born after 39 weeks, the ability of FLM testing to predict overall neonatal outcomes at a given gestational age is less clear. We hypothesized that among neonates at similar late-preterm or early-term gestational ages, mature pulmonary testing would not serve as a surrogate of overall fetal maturity. Specifically, we sought to investigate overall neonatal outcomes through a direct comparison of those neonates with mature fetal lung status to those with immature or transitional status in the critical gestational age where FLM testing is routinely performed.

## Materials and Methods

We conducted a retrospective cohort study of all women with a singleton, non-anomalous pregnancy undergoing FLM testing after amniocentesis and delivery at a single tertiary care center from January 2004 to December 2004 and January 2006 to December 2006. This time period was selected based on data available to the authors from detailed chart abstraction at the predetermined analysis point. This study was approved by the Human Subjects Division of the University of Washington. Data were derived from direct review of the electronic medical records of women and their newborns as detailed below. All chart abstraction was performed by one of the authors (JV, SP, or EG). Discrepancies regarding abstraction outcomes were resolved in consultation with a fourth author (HG). Exclusion criteria were multiple gestation, delivery at or after 39 weeks gestation, fetal anomalies, vaginal sample collection, or collection interval greater than seven days prior to delivery.

All FLM testing was performed with a previously validated in-house fluorescence polarization assay using a commercial clinical laboratory TDx analyzer (Abbott Laboratories).<sup>11</sup> Pregnancy outcomes for two groups of women with FLM testing within one week of delivery were compared: 1) immature or transitional FLM status and 2) mature FLM status. Both groups were identified from laboratory records and verified by direct chart review.

FLM indices were abstracted including the gestational age at the time of testing. Maternal characteristics including age, parity, race, dating criteria, comorbidities including (pregestational and gestational) diabetes and chronic hypertension, medications, delivery indication, and mode of delivery were abstracted. All subjects underwent first- or second-trimester sonographic confirmation of gestational age by criteria recommended by the American College of Obstetricians and Gynecologists.<sup>12</sup>

Extensive information was gathered from neonatal charts including daily progress notes, laboratory and radiologic studies, transfer and discharge summaries with the goal to identify any outcome that required clinical intervention. A broad range of clinically relevant neonatal morbidities was considered, excluding outcomes without direct impact on clinical management. Neonatal outcomes examined included death, respiratory outcomes, infectious complications, neurologic abnormalities, gastrointestinal outcomes, metabolic abnormalities, cardiovascular complications, and hematologic problems. Specifically, respiratory outcomes included respiratory distress syndrome (RDS), transient tachypnea of the newborn, bronchopulmonary dysplasia, persistent pulmonary hypertension, need for respiratory support (including ventilatory support or any other mode of oxygen supplementation), and use of surfactant. Infectious outcomes included proven sepsis and pneumonia. Evaluation for possible infection, including antibiotic administration, was examined but not included in the composite outcome as this is the highest incidence intervention in late preterm births.<sup>3</sup> Neurologic outcomes included intraventricular hemorrhage, generalized seizures requiring treatment, hypoxic ischemic encephalopathy, and periventricular leukomalacia. Gastrointestinal outcomes included feeding difficulties requiring hyperalimentation or enteral tube feeding. Hepatobiliary outcome included jaundice requiring phototherapy. Cardiovascular outcomes included arrhythmia or need for neonatal echocardiography. Hematologic outcomes included blood transfusion and thrombocytopenia requiring treatment. The metabolic outcome examined was hypoglycemia requiring intravenous glucose administration.

The primary outcome was a composite of any of these neonatal outcomes that required clinical intervention. In addition, NICU admission and NICU length of stay were examined. The primary outcome was compared between subjects with mature FLM status versus those subjects with immature/transitional FLM indices.

A power analysis was not feasible due to unknown proportions with specifically defined composite outcomes. Descriptive characteristics were compared using  $\chi^2$  for dichotomous variables. Student t tests or Mann Whitney U were used for comparison of continuous variables as appropriate. We made an *a priori* decision to adjust for the following confounders using logistic regression: maternal age, race/ethnicity, gestational age, and mode of delivery.

## Results

There were a total of 388 recorded births with FLM testing in the study period. After applying exclusion criteria (Figure 1), a total of 234 mother-neonate dyads were available for analysis. Of these, 46/234 (19.7%) had immature/transitional FLM results within one

week of delivery, and 188/234 (80.3%) had mature FLM results within one week of delivery.

Maternal pregnancy characteristics in the mature and immature/transitional testing groups are presented in Table 1. Mean gestational age at time of fetal lung maturity testing was  $36.8 \pm 1.3$  weeks in the mature group compared to  $35.7 \pm 2.1$  weeks in the immature/transitional group. Mean birthweight for the mature group was  $3036 \pm 673$  grams compared to  $2486 \pm 691$  grams in the immature/transitional group. The mean latency from time of testing until delivery was  $3.1 \pm 2.3$  days in the immature/transitional group compared to  $1.3 \pm 1.2$  days in the mature group.

Among the immature/transitional group, 14/46 (30.4%) were delivered between 37 and 38 6/7 weeks gestation, 23/46 (50%) were delivered between 34 and 36 6/7 weeks gestation, and 9/46 (19.6%) were delivered prior to 34 weeks gestation. Among the mature testing group, 105/188 (55.9%) were delivered between 37 and 38 6/7 weeks gestation, 78/188 (41.5%) were delivered between 34 and 36 6/7 weeks gestation, and only 5/188 (2.7%) were delivered prior to 34 weeks gestation.

There were no perinatal deaths. The primary composite adverse neonatal outcome occurred more often in the immature/transitional group (25/46, 52.2%) than in the mature group (61/188, 32.4%). Prior to adjustment for confounders, the odds of experiencing the primary outcome in the immature/transitional group was approximately two-fold greater than that of the mature group; unadjusted odds ratio (OR) 2.3 (95% confidence interval [CI] 1.2-4.4). However, after adjusting for confounding variables including gestational age, maternal age, maternal race, and mode of delivery, the odds of experiencing the primary composite neonatal adverse outcome was not significantly different among the groups; adjusted OR 1.4 (CI 0.7-3.0) (Table 2).

There was a significant inverse relationship between gestational age and the composite outcome ( $p < 0.001$ ). In the group with immature/transitional testing results, the composite outcome occurred in 77.8%, 65.2%, and 14.3% of neonates born prior to 34 weeks, 34 to 36 6/7 weeks, and 37 to 38 6/7 weeks gestation, respectively. In the group with mature testing results, the composite outcome occurred in 80%, 44.9%, and 20.9% of neonates, respectively. The sample size and composite morbidity for each group by gestational age are represented in Figure 2.

Prior to adjustment, there was a significant difference in the percentage of NICU admissions; 46.7% in the immature/transitional group admitted and 21.3% in the mature, OR 3.0 (CI 1.5-5.9). After adjustment, this finding was no longer significant, aOR 1.9 (CI 0.9-4.1). Similarly, median length of stay was not significantly different between the two groups: median 7 days (range 1-48 days) in the mature group and median 9 days (range 1-34 days) immature/transitional.

As expected, the rate of respiratory distress syndrome was significantly higher in the immature/transitional group; OR 3.4 (CI 1.1-10.3). Grouping neonatal morbidities by system (results summarized in Table 2) revealed significant differences prior to adjustment in gastroenterological complications (primarily feeding difficulties requiring treatment), OR

4.4 (CI 2.0-9.8). After adjustment for confounders, this difference was no longer significant. No significant differences were noted for overall adverse hepatobiliary, respiratory, infectious disease, neurologic, cardiac, metabolic, and hematologic outcomes.

In the subset of mothers with diabetes (52/234, 22%), after adjustment for confounders, fetal lung maturity status was not associated with composite neonatal morbidity.

## Comment

Both mature and immature FLM groups had high levels of composite adverse neonatal outcomes. While the unadjusted rate of clinically significant complications was increased among the transitional/immature group, this difference was not present after adjustment for potentially confounding variables including gestational age. Our findings validate previously published studies demonstrating a significant decrease in the rate of RDS in the setting of mature FLM testing but also demonstrate that this decrease does not extend to broader morbidity.<sup>11, 13, 14</sup>

Prior work by Bates, Dola, and others has provided important information regarding outcomes of late preterm/early term neonates with mature FLM compared to those delivered after 39 weeks gestation.<sup>2-6</sup> To add to this literature, we sought to assess outcomes by FLM status among neonates at similar gestational ages in the late preterm and early term time periods. We believe our findings help place RDS within a larger context of short and long-term adverse outcomes associated with late preterm birth.<sup>7, 15-17</sup> In our population, both RDS and composite adverse neonatal outcomes decreased as gestational age increased. Our data add to the evolving literature that supports delaying delivery until 39 weeks gestation when no immediate maternal or fetal risk is present.<sup>2-6,13,14</sup>

While the strength of our study design lies in the ability to directly compare subjects with different FLM status at the same gestational age, this design also increases the likelihood that subjects with immature/transitional status were delivered due to an incident maternal or fetal indication. While this may introduce a bias toward amplification of morbidity in the immature/transitional group, the direction of such a bias would be against our hypothesis that general morbidity would not differ between groups.

Other major strengths of our study include a large and representative sample size, a clinically diverse population potentially allowing for generalizability of our results to other populations, and an *a priori* defined primary outcome which limits the potential for multiple comparisons. We also acknowledge several limitations. A retrospective study design limits the ability to identify and correct potential misclassification of neonatal outcomes and maternal characteristics. Confounding remains a possibility in the absence of a randomized study design. As term uncomplicated newborns receive care in a newborn nursery whereas preterm infants often receive care in a neonatal intensive care unit, the distribution of intervention may reflect recording bias or practice variation between services. Additionally, our study was not powered to specifically analyze singular adverse outcomes such as stillbirth. Finally, we were unable to study long-term neonatal outcomes associated with the use of FLM studies, notably neurodevelopmental consequences. FLM testing was performed

by fluorescence polarization. We would expect similar results with comparable FLM tests.<sup>1,11</sup>

Overall, we found that mature and transitional/immature FLM status was not correlated with the spectrum of neonatal morbidities in late preterm and early term births. In our population, neonatal complications requiring clinical intervention remained common despite mature FLM testing. As our knowledge of the complexity of fetal and neonatal maturation evolves, the limitations of the singular focus of FLM testing are clear. Thus, our study supports the idea that FLM status should be one consideration amongst many complex, sometimes unmeasurable, markers of global maturation. The obstetric balance between continued *in utero* gestation versus delivery should continue to give us pause.

Future studies may identify specific patient populations where a significant difference in outcome with documented FLM exists. Biomarkers predictive of non-respiratory adverse events, including neurodevelopmental outcomes, in late preterm/early term birth represent an important area of future research focus.

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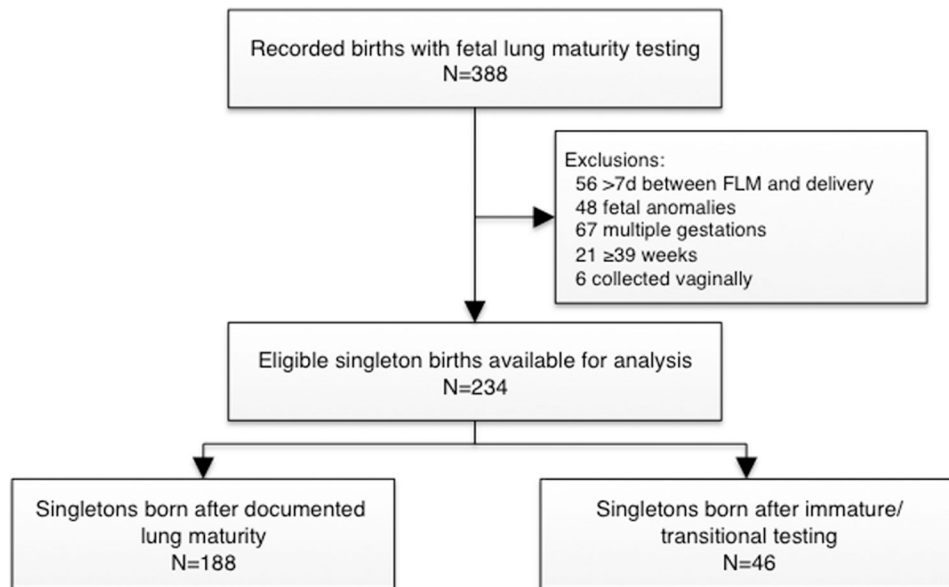
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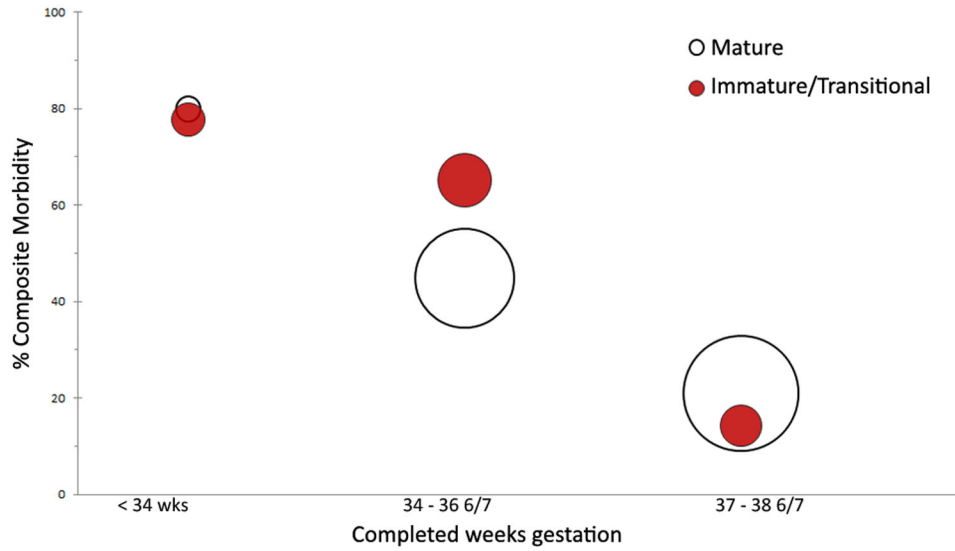
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**Figure 1.**  
Flow chart indicating exclusions.





**Figure 2.**

Bubble chart demonstrates mature results (unfilled) and immature/transitional results (filled). The circle diameter represents relative sample size. The location of the circle indicates the % neonatal composite morbidity encountered (y-axis) at different gestational ages (x-axis). In the group with immature/transitional testing results, the composite outcome occurred in 77.8%, 65.2%, and 14.3% of neonates born prior to 34 weeks, 34 to 36 6/7 weeks, and 37 to 38 6/7 weeks gestation, respectively. In the group with mature testing results, the composite outcome occurred in 80%, 44.9%, and 20.9% of neonates, respectively.

**Table 1**  
**Clinical characteristics of included subjects<sup>a</sup>**

Demographic Variable	Mature(n=188)	Transitional/Immature (n=46)	p value
Maternal age (years)	31.8 ± 7.0	31.6 ± 7.4	0.86
Race (% Caucasian)	101 (53.7%)	26 (56.5%)	0.56
Gravidity	3.1 ± 2.1	3.6 ± 2.1	0.12
Parity	1.2 ± 1.2	1.4 ± 1.3	0.21
Gestational age at FLM testing (weeks)	36.8 ± 1.3	35.7 ± 2.1	0.0004
Latency to delivery (days)	1.3 ± 1.2	3.1 ± 2.3	<0.0001
Birthweight (grams)	3036 ± 673	2486 ± 691	<0.0001
Mode of delivery (% Cesarean section)	136 (72.3%)	31 (67.4%)	0.58
Medical Comorbidity	105 (55.9%)	26 (56.5%)	0.94
- Diabetes <sup>b</sup>	43 (22.9%)	9 (19.6%)	0.63
- Hypertension	43 (22.9%)	14 (30.4%)	0.28

<sup>a</sup>Results expressed as mean ± standard deviation or N (%)

<sup>b</sup>Includes pregestational and gestational diabetes

**Table 2**  
**Selected neonatal complications by fetal lung maturity result**

System	Frequency in mature	Frequency in transitional/immature	OR (95% CI)	Adjusted OR <sup>b</sup> (95% CI)
<b>Composite</b>	<b>61/188 (32.5%)</b>	<b>24/46 (52.2%)</b>	<b>2.3 (1.2-4.4)</b>	<b>1.4 (0.7-3.0)</b>
GI	17/188 (9.0%)	14/46 (30.4%)	4.4 (2.0-9.8)	2.5 (1.0-6.2)
Hepatobiliary	35/188 (18.6%)	12/46 (26.1%)	1.5 (0.7-3.3)	0.7 (0.3-1.7)
Respiratory <sup>a</sup>	15/188 (8.0%)	8/46 (17.4%)	2.4 (1.0-6.1)	1.4 (0.5-4.1)
ID	13/188 (6.9%)	6/46 (13.0%)	2.0 (0.7-5.6)	0.9 (0.3-2.9)
Neuro	5/188 (2.7%)	2/46 (4.4%)	1.7 (0.3-8.9)	0.8 (0.1-5.8)
Cardiac	6/188 (3.2%)	2/46 (3.4%)	1.4 (0.3-7.1)	0.5 (0.1-4.3)
Metab	13/188 (6.9%)	2/46 (4.4%)	0.6 (0.1-2.8)	0.6 (0.1-2.9)

<sup>a</sup> Overall respiratory morbidities

<sup>b</sup> After adjustment for gestational age, maternal age, maternal race, and mode of delivery