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Neonatal Outcomes of Elective Early Term Births after Demonstrated Fetal Lung Maturity

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Abstract

Background: Studies of early term birth after demonstrated fetal lung maturity show that respiratory and other outcomes are worse with early term birth (37⁰–38⁶) even after demonstrated fetal lung maturity when compared with full term birth (39⁰–40⁶). However these studies included medically indicated births and are therefore potentially limited by confounding by the indication for delivery. Thus the increase in adverse outcomes might be due to the indication for early term birth rather than the early term birth itself.

Objective: We examined the prevalence and risks of adverse neonatal outcomes associated with early-term birth after confirmed fetal lung maturity as compared with full term birth in the absence of indications for early delivery.

Study Design: Secondary analysis of an observational study of births to 115,502 women in 25 hospitals in the United States from 2008–11. Singleton non-anomalous births at 37–40 weeks with no identifiable indication for delivery were included; early term births after positive fetal lung maturity testing were compared with full-term births. The primary outcome was a composite of death, ventilator for ≥ 2 days, CPAP, proven sepsis, pneumonia or meningitis, treated hypoglycemia, hyperbilirubinemia (phototherapy) and 5 min Apgar <7. Logistic regression and propensity score matching (both 1:1 and 1:2) were used.

Results: 48,137 births met inclusion criteria; the prevalence of fetal lung maturity testing in the absence of medical or obstetric indications for early delivery was 0.52% (n=249). There were 180

(0.37%) early-term births after confirmed pulmonary maturity and 47,957 full-term births. Women in the former group were more likely to be non-Hispanic White, smoke, have received antenatal steroids, have induction and have a cesarean. Risks of the composite (16.1% vs. 5.4%; adjusted odds ratio 3.2; 95% CI 2.1–4.8 from logistic regression) were more frequent with elective early term birth. Propensity scores matching confirmed the increased primary composite in elective early-term births: adjusted odds ratios 4.3 (1.8–10.5) for 1:1 and 3.5 (1.8–6.5) for 1:2 matching. Among components of the primary outcome, CPAP use and hyperbilirubinemia requiring phototherapy were significantly increased. Transient tachypnea of the newborn, neonatal intensive care unit admission and prolonged neonatal intensive care unit stay (>2 days) were also increased with early term birth.

Conclusions: Even with confirmed pulmonary maturity, early term birth in the absence of medical or obstetric indications is associated with worse neonatal respiratory and hepatic outcomes compared with full-term birth, suggesting relative immaturity of these organ systems in early term births.

Condensation

Early-term birth after pulmonary maturity in the absence of indications for early delivery is associated with a higher risk of neonatal morbidity compared with full-term birth.

Keywords

Early-term births; elective delivery; fetal lung maturity testing; neonatal outcomes

Introduction

For neonates born in the preterm (<37 weeks) or early term (37⁰–38⁶ weeks) period, positive fetal lung maturity testing is associated with decreased risk for respiratory neonatal morbidity compared to gestational age matched cohorts delivered without testing.¹ Tests used for fetal lung maturity evaluate markers of pulmonary development such as lecithin-sphingomyelin ratio, phosphatidylglycerol, fluorescence polarization, and lamellar body counts.¹ Several studies suggest that respiratory and other outcomes are worse with early term birth even after demonstrated fetal lung maturity when compared with full term (39⁰–40⁶ weeks) birth, a period associated with a nadir in neonatal risks.^{2–5} As a result, the role of fetal lung maturity testing in determining early term and preterm births has been deemphasized.⁶ Once widely used and recommended by ACOG as an indication for delivery prior to 39 weeks, the use of fetal lung maturity has declined in recent years.^{7–8} However, the conclusions from studies that have compared outcomes of preterm or early-term births after fetal lung maturity testing to those of full-term births are limited by the inclusion of pregnancies with indications for early term birth such as hypertension and diabetes which are themselves associated with adverse pregnancy outcomes. Therefore, it is possible that the indication for the early term birth (i.e., confounding by indication) and not the gestational age may explain the association with worse outcomes. The potential for residual confounding by indication remains despite adjustment for the common indications. Few studies have examined the outcomes of early-term births with positive fetal lung maturity testing vs. full term births in pregnancies without medical or obstetric indication for early

delivery. Therefore, we undertook this study to estimate the frequency and compare the risks of adverse neonatal outcomes with early term birth after positive fetal lung maturity testing compared to full term birth in the absence of indications for early delivery.

Materials and Methods

This is a secondary analysis of the Assessment of Perinatal Excellence (APEX) observational study of the *Eunice Kennedy Shriver* Maternal-Fetal Medicine Units Network.⁹ The APEX database includes detailed information on births to 115,502 women at 25 hospitals in the US from 2008–2011. The information was abstracted by chart review conducted by certified research staff at each center with IRB approval. The current study population included only singleton non-anomalous births at 37–40 weeks with no identifiable indication for early term delivery. Therefore, excluded were births to women with any medical or obstetrical indications for early delivery including: preeclampsia, eclampsia, gestational hypertension, or complicated chronic hypertension, oligohydramnios, prior classical, cesarean delivery or prior myomectomy, placenta previa or placenta accreta, fetal growth restriction, pregestational or gestational diabetes, placental abruption, chorioamnionitis, premature rupture of membranes, cholestasis of pregnancy, alloimmunization of pregnancy and fetal or congenital malformations.

Early-term births (at 37–38 completed weeks) after amniocentesis and confirmation of fetal lung maturity using the standard testing available at each center were the main study group. They were compared with full-term births (at 39–40 week of gestation) associated with a nadir in neonatal risks.

The primary study outcome was a perinatal composite previously associated with early term delivery, defined as one or more of the following: death before hospital discharge, need for respiratory support (ventilator for two or more days, CPAP or surfactant), proven newborn sepsis, pneumonia, meningitis, hypoglycemia requiring treatment, hyperbilirubinemia requiring phototherapy and/or 5 min Apgar <7. Proven newborn sepsis required positive blood culture results or clinical picture of sepsis syndrome in the setting of infection, pneumonia required X-ray confirmation and meningitis required a culture positive cerebrospinal fluid. Secondary outcomes included the components of the primary composite and specific neonatal respiratory or neonatal morbidities that have either been associated with early delivery or fetal lung maturity testing including respiratory distress syndrome, transient tachypnea of the newborn, cardiopulmonary resuscitation with first 24 hours, bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn, necrotizing enterocolitis, intraventricular hemorrhage, seizures, NICU admission, hypoxic ischemic encephalopathy and meconium aspiration. The definitions of these outcomes were based on the clinical neonatology diagnoses abstracted from the chart.

Demographic and other characteristics of the study groups were compared using chi-square, Fisher exact, t-tests and Wilcoxon rank tests as appropriate. Similar tests also were used for univariable analyses of outcomes. Prior to multivariable analyses we assessed for effect modification by stratifying the primary outcome results by quality of pregnancy dating (based on trimester of confirmatory ultrasound), prior administration of antenatal steroids,

labor type and mode of delivery. Logistic regression and also propensity score matching (1:1 and 1:2 matching of early-term with lung maturity testing to full-term on a range of covariates) were used to evaluate the independent relationships in multivariable regression analyses. Propensity scores matching were used as an alternative method to usual logistic regression for estimating the effect of the policy of fetal lung maturity testing from the observational data. Propensity scores is a multivariable analysis methodology that stratifies patients based on probability of receiving an intervention controlling for measured confounding, and may provide a more robust assessment of the relationship between the early delivery after lung maturity testing and outcomes. While 1:1 matching would afford better control for confounding, 1:2 matching would afford more power for the adjustments. The potential confounders (matching factors) considered for both logistic regression and propensity scores analyses respectively included age, parity, BMI, race/ethnicity, mode of delivery, type of labor, smoking, antenatal steroids, quality of dating, neonatal sex, parity and BMI. We did not adjust for type of labor since it is in the intervening pathway and is closely correlated with mode of delivery. Conditional logistic regression models were used in the matched propensity score analysis. SAS version 9.3 was used for the analyses. For all comparisons a p-value <0.05 was considered statistically significant; no adjustments were made for multiple comparisons as there was a clearly identified primary outcome of interest.

Results

A total of 48,137 singleton pregnancies out of the 115,502 pregnancies (118,422 babies) in the APEX database met the inclusion criteria for this study (see Figure 1 for flow of inclusion and exclusion criteria). Of note, 365 women who underwent fetal lung maturity testing were among the 40,904 excluded due to medical or obstetric indications; 93 with negative and 272 with positive fetal lung maturity testing at 37–38 weeks. The overall prevalence of fetal lung maturity testing in the absence of medical or obstetric indications for early delivery in the study cohort was 0.52% (n=249). There were a total of 180 (0.37%) early term births after positive fetal lung maturity testing. The 47,957 full-term births included 69 who had prior fetal lung maturity testing (42 mature and 27 immature). Of the early term births, 115 (63.9%) were at 37 weeks and 65 (37.1%) at 38 weeks; of full term births, 29070 (60.6%) were at 39 weeks and 18887 (39.4%) at 40 weeks.

The characteristics of the two study groups are presented in Table 1. Parity, BMI and neonatal sex were similar between groups. Mothers of early-term births who had positive fetal lung maturity testing were more likely to be non-Hispanic White, have dates confirmed by first trimester ultrasound or ART, smoke during pregnancy, and have received antenatal steroids.

The results of univariable analyses showing the frequency of each study outcome by group and the unadjusted relative risk relative to full-term births are presented in Table 2. The primary composite outcome (16.1% vs. 5.4%) was more frequent in the early-term group with fetal lung maturity testing. When examined by completed week of gestation, the primary outcome frequency was 20% at 37 weeks, 9.2% at 38 weeks, 5.3% at 39 weeks and 5.6% at 40 weeks. Respiratory support with CPAP and hyperbilirubinemia requiring phototherapy were the most frequent components of the primary composite and both were

more frequent in the early term birth with positive lung maturity group compared with the full-term birth group. Transient tachypnea of the newborn and NICU stay were also more frequent in the early term group (see Table 2). All 8 perinatal deaths (all stillbirths) were in the fullterm group, but no outcome (including perinatal death) was statistically significantly more frequent in the full-term group. Furthermore, none of the 8 stillbirths were born to any of the 69 women who delivered at full term with prior fetal lung maturity testing including 27 with immature results.

In stratified analyses (results not shown), the incidence of the primary composite outcome was higher in the early-term group with positive fetal lung maturity testing regardless of quality of pregnancy dating (based on trimester of confirmatory ultrasound), prior administration of antenatal steroids, labor type and mode of delivery. None of these variables was therefore included in multivariable analyses as an effect modifier. Adjusted results from logistic regression analyses (see Table 3) confirmed the unadjusted findings: the primary composite outcome (aOR 3.2, 95% CI 2.1-4.8), hyperbilirubinemia requiring phototherapy and NICU admission and stay were all significantly increased with early term birth even after confirmed fetal lung maturity compared with full-term births. Analyses by propensity scores matching also confirmed the increase in the primary composite with early term delivery after confirmed fetal lung maturity: ORs 4.3 (1.8-10.5) for 1:1 matching and 3.5 (1.8-6.5) for 1:2 matching. When we restricted the analysis to only those with reliable dating (supported by first or second trimester ultrasound) (aOR 3.1 (2.2-4.4)) or without antenatal corticosteroids (aOR 3.1; 2.2-4.3), the primary outcome results were consistent with those from our main analysis.

We conducted supplementary analyses including an additional 2191 with full-term deliveries that had been excluded due to gestational hypertension, preeclampsia and eclampsia bringing the number of full-term deliveries to 50,148. The primary outcome results remained essentially unchanged overall (aOR 3.1; 2.1-4.7) and when stratified by mode of delivery – vaginal (aOR 2.7; 1.4-5.6) and cesarean (aOR 3.4; 2.0-5.6).

Comment

We found that compared with full-term (39⁰–40⁶) births, elective early-term (37⁰–38⁶) births (i.e. births in the absence of obvious medical or obstetrical indications for early delivery) are associated with worse respiratory and other neonatal outcomes including hyperbilirubinemia requiring phototherapy. Our results also show that early delivery after fetal lung maturity testing is rare in contemporary obstetric practice. Furthermore, we demonstrate an important increase in other neonatal morbidities and NICU stay.

Our findings are consistent with those of reports suggesting that the practice of fetal lung maturity testing and early delivery if positive does not reduce the risk of adverse neonatal outcomes to the levels seen with delivery 39–40 weeks.^{2–5} The strength of the association of adverse neonatal outcomes following early-term delivery compared with delivery at 39–40 weeks in our study is also similar to findings from prior reports. In addition, our study differs from the prior studies in that we focused on elective deliveries, excluding any recognized medical or obstetric indications for early delivery. Therefore, our study is unique

in suggesting that the medical or obstetric indication for early delivery alone is not the major driver of adverse neonatal outcomes with early birth after positive lung maturity testing. The low prevalence overall of fetal lung maturity testing in our cohort confirms observations of decreased utilization of fetal lung maturity testing in recent years.^{8, 11–12} Although all 8 deaths (stillbirths) were observed in the full-term group, this is not surprising since fetal lung maturity testing is not done in the setting of stillbirths and because the size of the full-term group was so much larger. Although no stillbirth occurred in women who had prior fetal lung maturity testing, these data should not be interpreted to mean that fetal lung maturity testing would have prevented 8 stillbirths from occurring in the full-term group. Those with negative testing would be expectantly managed, with a risk of stillbirth that is not null. We lacked the power to assess this issue and other data suggest that neonatal, postneonatal and infant mortality may be increased with early term compared with full-term delivery.¹⁰

The strengths of our study include the following: indications for early delivery were excluded to minimize confounding by indication and the data were derived from a well-characterized database populated by certified research data collectors who conducted real-time chart abstractions around the time of delivery.⁹ This provides reassurance regarding the validity of our data. We do acknowledge some study limitations. First, while adequate for the primary composite outcome, the number of elective early-term deliveries is relatively small to fully delineate the association with less frequent outcomes such as perinatal death, respiratory distress syndrome and other neonatal morbidities. Second, because fetal lung maturity testing is not performed in the setting of stillbirths, all intrauterine deaths were observed in the full-term group. Furthermore, we do not have information on stillbirths in those who had negative fetal lung maturity testing, and therefore were expectantly managed. We have acknowledged the lack of power to demonstrate any differences in stillbirth between groups. We also did not have information regarding the specific lung maturity test used at each center for analysis; although the tests are expected to perform similarly at the cut-offs used for clinical purposes.¹ Third, we acknowledge that the alternative to purely elective early-term delivery is expectant management during which preeclampsia and other outcomes that may affect neonatal morbidity may occur and not always elective delivery at 39–40 weeks. However, the large majority of patients are delivered at 39–40 weeks and our data suggest that their newborns do better even when we included those who developed gestational hypertension and preeclampsia/eclampsia in supplementary analyses. Finally, we do not present any data on maternal outcomes or long-term maternal and infant outcomes. We do not anticipate that early-term delivery will be associated with better maternal outcomes compared with full term delivery; a prior study by our group using another cohort suggested that maternal outcomes may be similar or even be worse with early-term delivery compared to full-term delivery in patients undergoing repeat cesarean.¹³

Overall, our findings suggest that amniocentesis for fetal lung maturity testing should not be undertaken to guide purely elective early-term delivery. One role for lung maturity testing may be in the setting of uncertainty regarding the gestational age.⁶ There is an ongoing debate regarding the proper role for fetal lung maturity testing to guide early delivery when there are ongoing concerns about fetal well-being in the absence of a firm indication for early delivery.^{6,12} An example of this scenario is a patient with persistent perception of reduced fetal movement despite reassuring antenatal testing or one with a prior history of

fetal demise. Considering that newborns delivered after positive fetal lung maturity testing may be at lower risk of adverse fetal outcomes compared to gestational age-matched cohorts, it is argued fetal lung maturity testing may provide reassurance when the need to deliver is uncertain.^{1,12} Our findings do not specifically address such scenarios and patients with these characteristics were not specifically excluded from our study population. Ideally, a clinical trial in which pregnant women are either randomized to (or offered) fetal lung maturity testing versus the alternative (depending on the scenario) of delivery or expectant management until 39–40 weeks would provide answers regarding the best practice. However, in the absence of such data, our findings support recommendations against using amniocentesis to determine early delivery in the absence of medical or obstetrical indications or concern.⁶

Appendix.

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

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Figure 1: Flow chart of inclusion and exclusion criteria

A total of 48,137 singleton pregnancies out of the 115,502 pregnancies (118,422 babies) in the APEX database met the inclusion criteria for this study, most exclusions were due to indications for delivery.

Table 1.

Baseline Characteristics by Gestational Age at Delivery

	Early-term FLM*	Full-term (39–40)	
Baseline Characteristic			P val
	N=180	N=47957	
Age, yrs, median (min to max)	30.0 (18.0 to 56.0)	28.0 (12.0 to 57.0)	<0.001
BMI, kg/m ² , median (min to max)	30.6 (21.5 to 61.8)	29.7 (12.4 to 99.1)	0.950
Race/ethnicity			0.007
Non-hispanic white	112 (62.2)	23196 (48.4)	
Non-hispanic black	29 (16.1)	8762 (18.3)	
Non-hispanic asian	5 (2.8)	2582 (5.4)	
Hispanic	30 (16.7)	10851 (22.6)	
Other	3 (1.7)	2077 (4.3)	
Not specified	1 (0.6)	489 (1.0)	
Parity, median (min to max)	1.0 (0.0 to 9.0)	1.0 (0.0 to 11.0)	0.840
Mode of labor			<0.001
Induced	72 (40.0)	10351 (21.6)	
Spontaneous/augmented	6 (3.3)	30396 (63.4)	
Cesarean without labor	102(56.7)	7210 (15.0)	
Mode of delivery			<0.001
Vaginal	68 (37.8)	35540 (74.1)	
Cesarean delivery	112 (62.2)	12417 (25.9)	
Dating ultrasound trimester			<0.001
1st trimester or ART	111 (62.0)	20617 (43.0)	
2 nd or 3 rd trimester	55 (30.7)	22294 (46.5)	
None	13 (7.3)	5027 (10.5)	
Baby sex female	90 (50.0)	24085 (50.2)	0.953
Smoker	23 (12.8)	4035 (8.4)	0.033
Steroids for fetal lung maturity	6 (3.3)	228 (0.5)	<0.001

* Early-term FLM: delivery at 37–38 weeks after positive fetal lung maturity testing

Table 2.

The Incidence of the Primary Composite and Other Outcomes by Study Group and Un-Adjusted Results

Outcomes	Early-Term FLM	Full-term	RR (95% CI)	P value
	n=180	n=47957		
	n (%)	n (%)		
Primary composite outcome	29 (16.1)	2594 (5.4)	3.0 (2.1 – 4.2)	<0.001
Components:				
Perinatal death *	0 (0.0)	8 (0.02)		
Ventilation within 24 hours for 2 days	1 (0.6)	57 (0.1)	4.7 (0.7 – 35.6)	0.125
CPAP use	7 (3.9)	482 (1.0)	3.9 (1.9 – 8.0)	<0.001
Proven newborn sepsis	0 (0.0)	33 (0.1)		
Pneumonia	0 (0.0)	77 (0.2)		
Meningitis	0 (0.0)	0 (0.0)		
Treated hypoglycemia	1 (0.6)	161 (0.3)	1.7 (0.2 – 11.8)	0.615
Phototherapy for hyperbilirubinemia	17 (9.4)	1648 (3.4)	2.7 (1.7 – 4.3)	<0.001
Apgar <7 at 5 minutes	2 (1.1)	237 (0.5)	2.2 (0.6 – 9.0)	0.251
Secondary Outcomes				
Respiratory distress syndrome	1 (0.6)	118 (0.3)	2.3 (0.3 – 16.1)	0.416
Transient tachypnea of the newborn	14 (7.8)	679 (1.4)	5.5 (3.3 – 9.1)	<0.001
CPR within first 24 hours	0	19 (0.04)		
Bronchopulmonary dysplasia	0	1 (0.0)		
Persistent pulmonary hypertension of the newborn	0	38 (0.08)		
Necrotizing enterocolitis	0	5 (0.01)		
IVH	0	10 (0.02)		
Seizures	0	37 (0.1)		
NICU admission	23 (12.8)	2088 (4.3)	2.9 (2.0 – 4.3)	<0.001
NICU stay (range) **	4 (0–16)	2 (0 to 63)	N.A.	
NICU stay >2 days	14 (7.8)	869 (1.8)	4.3 (2.6 – 7.1)	<0.001
NICU length of stay > 2 (if admitted to nicu)	14/23 (60.9)	869/2088 (41.6)	1.5 (1.0 – 2.0)	0.025
Meconium aspiration	0	65 (0.1)		
Hypoxic-Ischemic Encephalopathy	0	61 (0.1)		

* All perinatal deaths were stillbirths

** Model tested was a general linear model and the model did not fit.

Table 3.

Independent Relationship Between Neonatal Outcomes and Elective Early Term Delivery

Outcome	AOR (95% CI) *
Composite Outcome	3.2 (2.1–4.8)
Components of Primary Outcome:	
Perinatal Death **	n/a
Ventilator support 2 days within 24 hrs	4.7 (0.7 – 36) †
CPAP	3.9 (1.91 – 8.0) †
Treated hypoglycemia (requiring NICU)	1.7 (0.2 – 11.8) †
Hyperbilirubinemia requiring treatment	3.0 (1.8–5.0)
Apgar <7 at 5 minutes	2.2 (0.6 – 9.0) †
Respiratory distress syndrome (RDS)	2.3 (0.3 – 16) †
Transient tachypnea of the newborn (TTN)	5.5 (3.3–9.1)
NICU admission	2.8 (1.8–4.5)
NICU Stay >2 days	4.3 (2.4–7.7)

* AOR=Adjusted Odds Ratio (adjusted for ethnicity, age, mode of delivery, smoking, antenatal steroids, quality of dating)

† Unadjusted RR retained due to small numbers (AORS are the results in bold);

** All perinatal deaths were stillbirths; n/a as unable to calculate due to zero cell