11 Fetal lung maturity and neonatal outcome >34 weeks: do antenatal steroids improve outcomes if administered after negative maturity results?

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OBJECTIVE: Following immature fetal lung indices, obstetricians may choose one of three clinical management strategies: (1) treat with antenatal corticosteroids (ACS) with subsequent planned delivery, (2) await repeat testing with mature indices, or (3) expectant management. We tested the hypothesis that the approach of ACS administration after fetal lung immaturity would not improve neonatal outcome in infants >34 weeks.

STUDY DESIGN: This retrospective cohort study compared outcomes of 365 infants born >34 weeks after fetal lung maturity testing: 102 had immature fetal lung indices and were treated with ACS followed by planned delivery within one week, 78 had immature fetal lung indices and were managed expectantly, and 185 delivered after mature amniocentesis. We analyzed differences between groups in a composite adverse neonatal outcome (NICU admission, ongoing respiratory support, phototherapy, antibiotic treatment, intravenous fluids for hypoglycemia, or gavage feeding) and a composite respiratory outcome (oxygen supplementation, continuous positive airway pressure, mechanical ventilation, or surfactant administration) by univariable and multivariable analyses.

RESULTS: Infants born after immature fetal lung indices followed by ACS therapy and delivery had significantly higher rates of neonatal morbidity, including oxygen supplementation, CPAP, hypoglycemia, and antibiotic treatment, compared to the other two groups ($p<0.05$). After adjusting for statistically influential and biologically plausible variables, infants managed expectantly were 90% less likely to have adverse respiratory outcome (aOR 0.1, 95% CI 0.01-0.9). Infants born after mature amniocentesis were 50% less likely to have adverse neonatal outcome (aOR 0.5, 95% CI 0.3-0.9) and 60% less likely to have adverse respiratory outcome (aOR 0.3, 95% CI 0.1-0.9).

CONCLUSION: Administration of ACS following immature fetal lung indices did not decrease rates of neonatal respiratory morbidity in infants born >34 weeks. As more mature infants had less neonatal morbidity, our study supports prolonging gestation until delivery is otherwise indicated.

Neonatal Outcome	Mature amniocentesis 34.0 to 38.6 weeks N = 185	Expectant management 34.4 to 40.0 weeks N = 78	Steroids after immature amnio 34.0 to 38.6 weeks N = 102	P
GA (weeks)	37.1 ± 1.0	38.2 ± 1.3	36.4 ± 1.1	<0.01
BW (kg)	3.1 ± 0.6	3.2 ± 0.6	2.8 ± 0.6	<0.01
Latency from amnio to delivery	1.7 ± 2.1	11.2 ± 11.6	4.6 ± 3.1	<0.01
Composite adverse neonatal outcome	27 (14.6%)	15 (9.2%)	27 (26.5%)	0.048
Composite respiratory outcome	6 (3.2%)	1 (1.3%)	10 (9.8%)	0.01
NICU admission	17 (9.2%)	8 (10.3%)	23 (22.6%)	<0.01

12 Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks–the PPROMEXIL-2 trial (ISRCTN05689407)

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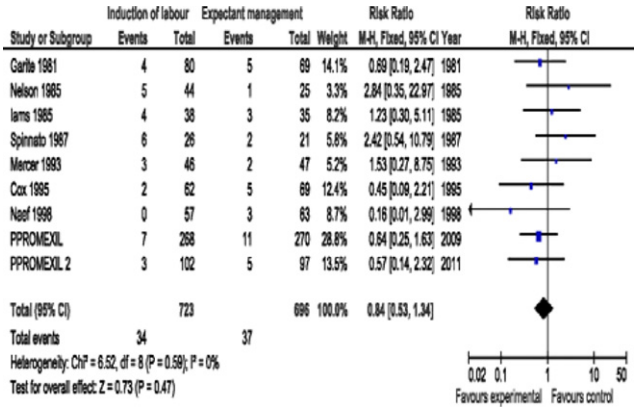
OBJECTIVE: PPROM is an important clinical problem. Our previous PPROMEXIL trial (ISRCTN29313500) compared the effectiveness of induction of labor (IL) to expectant management (EM) after PPROM between 34 and 37 weeks of gestational age (GA) in 532 pregnant women. This study showed that the incidence neonatal sepsis was low, and induction of labor did not reduce the risk of neonatal sepsis. Since the incidence of the primary outcome measure was lower than expected, we performed a second trial PPROMEXIL-2, aiming to randomize 200 patients.

STUDY DESIGN: The study was performed in a multicenter setting within the Dutch obstetric research consortium, in which 60 hospitals in the Netherlands collaborated. Pregnant women with prolonged (>24h) PPROM at a GA from 34 to 37 weeks, not in labor, were eligible. Patients were randomized to IL or EM. The primary outcome measure was neonatal sepsis, which was defined as a positive blood culture, biochemical infection parameters or clinical signs of infection. Secondary outcomes were among others, RDS, chorioamnionitis, and mode of delivery. In addition we performed a meta-analysis combining our data with previous studies.

RESULTS: Between December 2009 and January 2011, we randomized 199 women. Time between randomization and delivery was 1.6 days and 4.9 days (MD -3.2 days, 95%CI 2.1 to 4.4) after induction and expectant management, respectively. Neonatal sepsis was seen in 3 neonates (3.0%) in the IL-group versus 5 neonates (5.4%) in the EM-group (RR 0.55, 95%CI 0.14 to 2.2). There was one case of neonatal death in the IL-group, which was due to severe neonatal blood loss during delivery. There were no significant differences in other neonatal outcomes. Clinical chorioamnionitis was seen more often in the EM-group (4.1% vs 0%; $p=0.04$), whereas other maternal outcome and mode of delivery,were comparable. Meta-analysis of 1419 women included in 9 studies showed no difference in the risk of neonatal sepsis among treatment strategy (risk ratio .84 95%CI .53 to 1.3).

CONCLUSION: The risk of neonatal sepsis after PPROM near term is low. Induction of labor does not reduce this risk.



13 Method of delivery and neonatal outcomes in preterm, small for gestational age infants

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OBJECTIVE: Cesarean delivery (CD) has been proposed as an obstetric strategy to improve neonatal outcomes for premature fetuses with intrauterine growth restriction (IUGR). The relative rarity of this clinical situation has made prospective randomized studies challenging and has even limited retrospective cohort studies. This study was undertaken to compare neonatal outcomes by method of delivery in preterm (<34 week), small for gestational age (SGA) infants in a large diverse cohort.

STUDY DESIGN: Birth data for 1995 to 2003 from New York City were linked to hospital discharge data. Data were limited to singleton, live born, vertex neonates delivered between 25 and 34 weeks. Births complicated by known congenital anomalies, birth weight <500 grams and those requiring forceps or vacuum assistance were excluded. Deliveries were also excluded if there was a maternal history of prior CD. SGA was used as a surrogate for IUGR. Any diagnosis of intraventricular hemorrhage (IVH), seizure, sepsis, subdural hemorrhage, respiratory distress syndrome (RDS), or five minute Apgar <7 was considered a significant neonatal morbidity. Associations between method of delivery and neonatal morbidities were estimated using logistic regression.

RESULTS: 2560 SGA neonates meeting the study criteria were identified; 46% were delivered vaginally and 54% were delivered by CD. There was no significant difference in IVH, subdural hemorrhage, seizure or sepsis between the CD and vaginal delivery (VD) groups. CD compared to VD was associated with increased odds of RDS. The increased odds persisted after controlling for maternal age, ethnicity, education, primary payor, pre-pregnancy weight, gestational age at delivery, diabetes and hypertension. CD compared to VD was associated with increased odds of five minute Apgar <7 using unadjusted odds (odds ratio: 1.4; 95% CI 1.1-1.9), but this difference dissipated after adjusting for confounding factors.

CONCLUSION: CD was not associated with decreased odds of any neonatal complications and was associated with significantly higher odds of RDS in SGA preterm neonates.

Adjusted risk of adverse neonatal outcomes by mode of delivery, OR (95% CI)*

	SGA[§]		
	VD	CD	OR
Respiratory Distress Syndrome	270 (23.0)	435 (31.3)	1.3 (1.1-1.7)
Sepsis	37 (3.2)	47 (3.4)	1.1 (0.7-1.8)
Intraventricular hemorrhage	62 (5.3)	75 (5.4)	0.8 (0.6-1.3)
Subdural hemorrhage	5 (0.4)	14 (1.0)	1.7 (0.5-6.0)
Seizures	8 (0.7)	14 (1.0)	1.3 (0.5-3.5)
Five minute Apgar <7	79 (6.8)	130 (9.4)	1.3 (0.9-1.8)

* Adjusted for maternal age, ethnicity, education, primary payor, pre-pregnancy weight, gestational age at delivery, diabetes and hypertension
§ SGA defined as less than the 10th percentile

14 Effect of prescription medications on 17-alpha-hydroxyprogesterone caproate (17-OHPC) metabolism

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OBJECTIVE: 17-OHPC and certain prescription medications are metabolized by the CYP3A4 enzyme. We hypothesize that these medications may compete with 17-OHPC for metabolism. Any alteration in 17-OHPC metabolism may affect the concentration of 17-OHPC and impact its efficacy.

STUDY DESIGN: Pooled (n=5) human CYP3A4 microsomes were incubated for 60 min at 37C with 17-OHPC (2.5ug/mL) alone or in combination with 21 different medications known to be CYP3A4 substrates or inhibitors. Incubations were carried out in a solution of phosphate buffer and magnesium chloride. An NADPH-generating system was used to initiate metabolism. HPLC was performed to measure unmetabolized 17-OHPC concentration.

RESULTS: Thirteen of the 21 drugs tested exhibited inhibitory effects on 17-OHPC metabolism. 17-OHPC metabolism was inhibited by >80% when incubated with montelukast, esomeprazole, nelfinavir, or ritonavir. Metabolism of 17-OHPC was inhibited by 50-80% in the presence of fluconazole, itraconazole, voriconazole, sertraline, haloperidol, trazodone, tacrolimus, or bergamottin. Only 20-50% inhibition was observed in the presence of fluticasone.

CONCLUSION: 17-OHPC metabolism is inhibited by several prescription medications. Concomitant use of these medications during pregnancy may lead to significant alterations in 17-OHPC metabolism and ultimately impact the overall efficacy of 17-OHPC in the prevention of preterm birth. This work was supported by NICHD Obstetric-Fetal Pharmacology Research Units Network grant HD047905.

15 Bioinformatics analysis of biomarkers reveal differential maternal-fetal contributions to spontaneous preterm birth pathophysiology

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OBJECTIVE: To document racial disparity between African Americans (AA) and Caucasians (C) in pathophysiologic pathways and underlying disease functions associated with spontaneous preterm birth (PTB) induced by distinct maternal and fetal biomarker response.

STUDY DESIGN: 36 candidate biomarkers from PTB pathways were analyzed in maternal and fetal plasma from 191 subjects [105 PTB (<36 weeks): 59 AA and 46 C; 86 term births: 40 AA and 46 C (37-41 weeks)]. The contribution of dysregulated maternal and fetal biomarkers between PTB and term birth to distinct pathways were mapped using Ingenuity Pathway Analysis (IPA). Biomarkers that met the significance p-value cutoff of 0.2 (FDR correction) were matched within the IPA web application to determine attributing biological functions that were most enriched for each compartment and race. Fishers exact tests calculated the significance of the associations between biomarkers and biological functions (5.95E-04 to 2.78E-02).