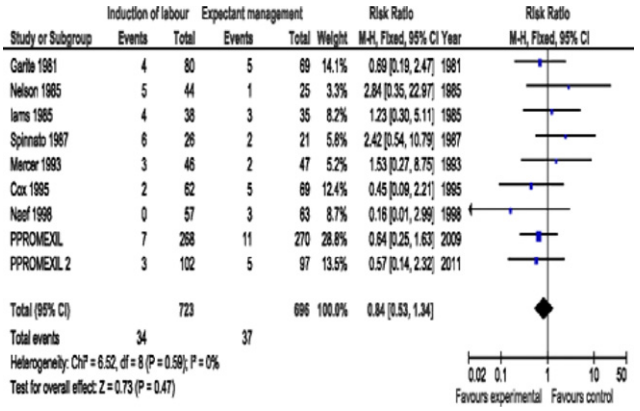


13 Method of delivery and neonatal outcomes in preterm, small for gestational age infants

Erika F. Werner[1], David Savitz[2], Teresa Janevic[3], Stephen F. Thung[4], Edmund F. Funai[4], Heather Lipkind[4]

[1]Johns Hopkins University, Gynecology and Obstetrics, Baltimore, MD, [2]Brown University, Departments of Epidemiology and Obstetrics and Gynecology, Providence, RI, [3]Yale University, Global Health Initiative, New Haven, CT, [4]Yale University, Ob/Gyn & Reprod Science, New Haven, CT

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

Yang Zhao[1], Courtney Cuppett[2], Steve Caritis[2], Raman Venkataramanan[1]

[1]University of Pittsburgh, School of Pharmacy, Pittsburgh, PA, [2]Magee-Womens Hospital, University of Pittsburgh, Maternal Fetal Medicine, Pittsburgh, PA

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

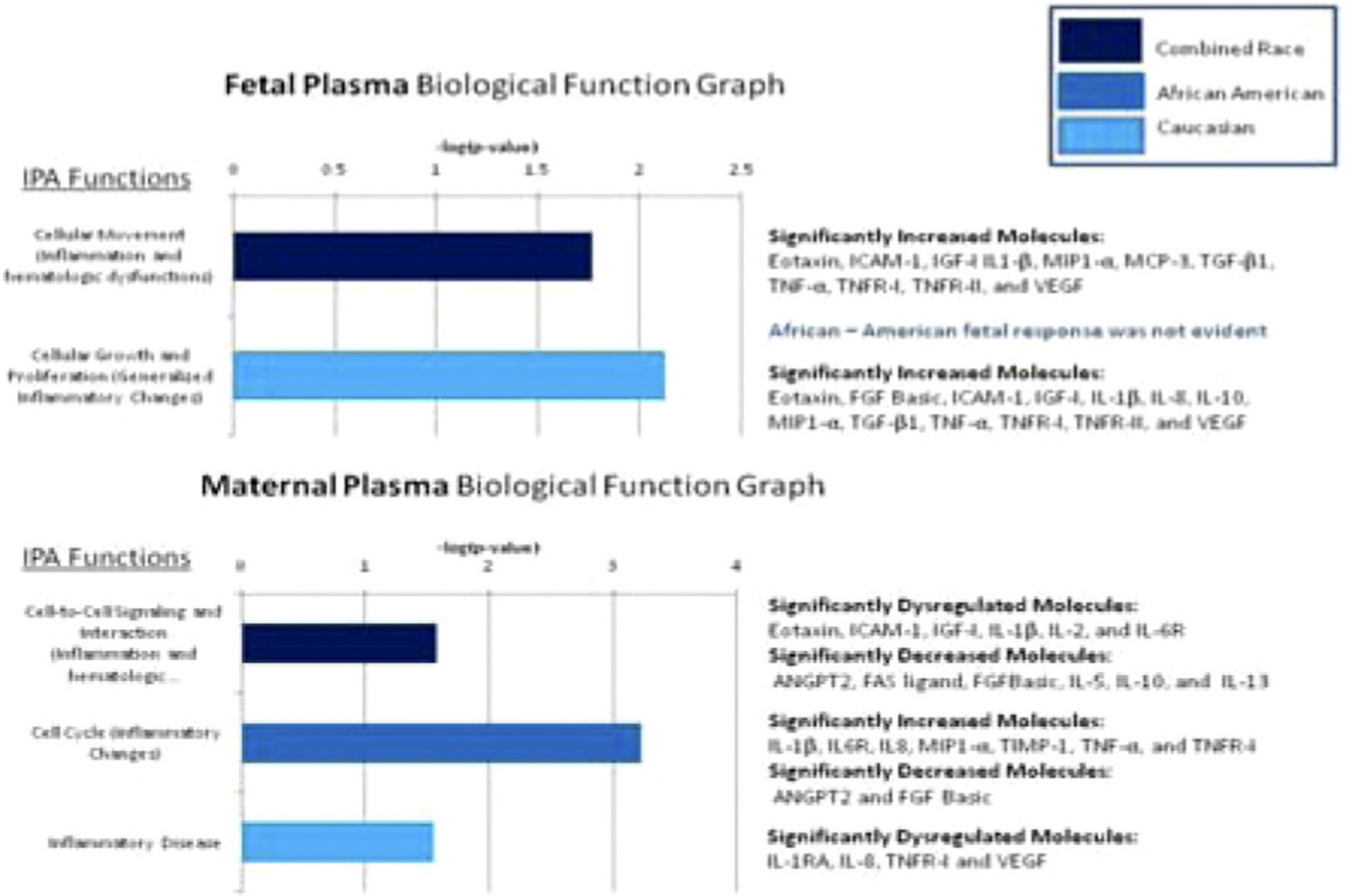
Geeta Bhat[1], Lina Brou[2], Cayce Drobek[1], Stephen Fortunato[2], George Saade[1], Ramkumar Menon[1]

[1]The University of Texas Medical Branch, Obstetrics and Gynecology, Galveston, TX, [2]The Perinatal Research Center, Maternal-Fetal Medicine, Nashville, TN

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).

RESULTS: In a combined analysis of races, IPA identified both fetal (Eotaxin,ICAM-1,IGF-I,IL-1β,MIP1α,MCP-3,TGFβ1,TNFα, TNFR-I,TNFR-II,VEGF) and maternal (Eotaxin,ICAM-1,IGF-I,IL-1β,IL-2,IL-6R,ANGPT2,FAS ligand,FGF Basic,IL-5,IL-10,IL-13) biomarkers of cellular movement and cell-to-cell interaction associated with PTB. Data stratified by race demonstrated fetal biomarkers (Eotaxin,FGF Basic,ICAM-1,IGF-I,IL-1β,IL8,IL-10 MIP1-α,TGF-β1,TNFα,TNFR-I,TNFR-II,VEGF) contribute to PTB in C (p= 4.53E-03). Fetal contribution was not evident in AA PTB. Maternal biomarkers (IL-1β,IL-6R,IL8,MIP1α,TIMP-1,TNF-α,TNFR-I, ANGPT2,FGF Basic) associated with AA PTB (p = 5.95E-04), and (IL-RA,IL8, TNFR-1,VGEF) associated with C PTB (p=2.78E-02).
CONCLUSION: Maternal-fetal biomarker differences result in distinct pathophysiologic pathways leading to PTB in different races. Markers of fetal inflammation and hematologic dysfunctions in C and maternal inflammatory markers in AA contribute to PTB. PTB biomarkers and pathways are not universal and may change based on individuals own risk factors including race.



16 Betamethasone dosing interval–12 or 24 hours apart?

Meena Khandelwal[1], Eric Chang[2], Clare Hansen[1], Krystal Hunter[3], Barry Milcarek[3]
[1]Cooper University Hospital, Obstetrics & Gynecology, Camden, NJ, [2]Camcare Associates, Obstetrics & Gynecology, Camden, NJ, [3]Cooper University Hospital, Cooper Research Institute, Camden, NJ

OBJECTIVE: To determine whether there is a statistically significant difference in the incidence of neonatal Respiratory Distress Syndrome (RDS) when administering 2 intramuscular maternal doses of 12 mg betamethasone 12 hours versus 24 hours apart. The total dosage of 24mg was based on animal studies and shown to achieve fetal concentrations comparable to stress levels of cortisol occurring after birth. The 24-hour dosing interval was arbitrarily selected. The 12-hour dosing maybe more appealing pharmakokinetically and clinically as one-third women with preterm labor deliver within 24 hours.
STUDY DESIGN: Prospective, randomized, semi-blinded trial. Women with spontaneous or medically-indicated preterm labor, with or without rupture of membranes, between 23 to 34 weeks were allocated into 4 groups and consented (Table). Each group was randomly assigned to the 12 or 24-hour dosing. RDS was defined as need for supplemental oxygen to maintain PaO2 >50 mm Hg with chest radiograph findings of RDS or need for surfactant therapy. Maternal blood was collected 48 hours after first dose; cord blood was collected at delivery for measuring betamethasone levels.
RESULTS: The incidence of RDS was significantly lower with the 12-hour dosing interval in mothers ≤26 weeks at enrollment. There was no difference noted in any other neonatal outcome (hospital days, mortality, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, retinopathy or intraventricular hemorrhage). There was no difference in incidence of maternal temperature >100.4 F or postpartum length of stay. Demographics are outlined in Table with no difference in groups except more black women in 24-hour Group A.
CONCLUSION: The 12-hour dosing interval is equivalent, and maybe superior, than the 24-hour interval for prevention of RDS in neonates of mothers delivering preterm. No difference was seen after 26 weeks probably due to the lower incidence of RDS and relatively smaller sample size. Black race is associated with lower incidence of RDS and is not a confounding factor. A larger multicenter prospective study is needed to confirm our findings.