GENERAL

Abstracts 36 – 43

Moderators: Thomas Garite, MD; Mary D'Alton, MD; Vincenzo Berghella, MD

36 Effect of in utero alcohol exposure on the expression of antioxidant enzymes in a mouse model of fetal alcohol syndrome

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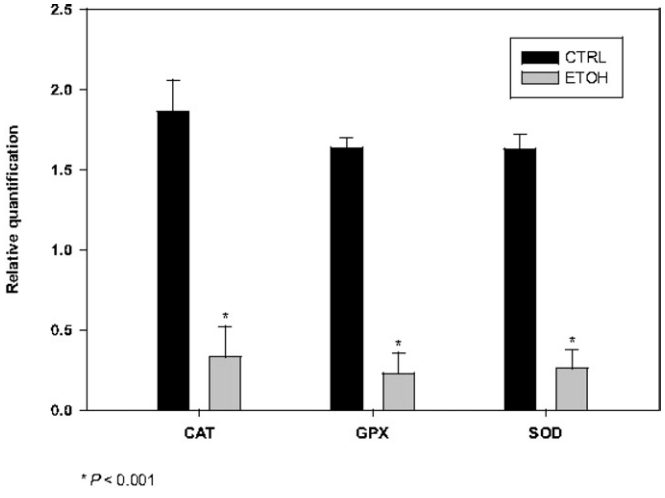
OBJECTIVE: Fetal alcohol syndrome (FAS) is the most common non genetic cause of mental retardation. Oxygen consumption in the brain results in generation of free radicals and this effect is magnified in response to alcohol. Antioxidative enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) function to prevent the cellular damage produced by free radicals. Our objective was to evaluate the effect of prenatal alcohol on antioxidant enzyme expression.

STUDY DESIGN: A well-characterized FAS model was used (Webster, 1980). Timed, pregnant C57BL6/J mice were treated on gestational day 8 (E8) with intraperitoneal injection of saline (control) or alcohol (0.03 mL/g). Pups were harvested on gestational day 18 (E18), their brains extracted and homogenized. Each fetal brain was analyzed individually for mRNA expression of SOD, GPx and CAT using real-time PCR with 18S for internal control. Student t test was used for statistical analysis (significance: $p<0.05$).

RESULTS: 25 pups from 4 litters in the alcohol group and 23 pups from 5 litters in the saline group were analyzed. There was no difference in maternal or pup weight between the two groups. SOD, GPx and CAT mRNA expression was significantly lower in the alcohol group compared to controls (Figure, $p<0.001$).

CONCLUSIONS: Prenatal alcohol exposure inhibits SOD, GPx and CAT expression. The reduction in these antioxidant enzymes promotes an oxidant environment and contributes to the cytotoxicity associated with FAS. The antioxidant system may be a novel pathway to target for prevention of the long term morbidity of FAS.



37 Maternal 25(OH)D levels and sFLT-1/PlGF ratio improves predictability of severe preeclampsia in early pregnancy

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OBJECTIVE: Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. It remains uncertain whether altered angiogenic factor activity in patients with preeclampsia is a result of the current disease state or if it was present before the development of preeclampsia. Recent studies have shown that low serum 25-hydroxyvitamin D (25[OH]D) level is a risk factor for preeclampsia. The clinical significance of in vitro findings that vitamin D regulates vascular endothelial growth factor (VEGF) production is unclear. We sought to determine if there is an association between second trimester maternal serum 25(OH)D levels and angiogenic factor activity and to compare their predictability of preeclampsia.

STUDY DESIGN: We conducted a nested case-control study of pregnant women with severe preeclampsia ($n=41$) versus women with uncomplicated term birth ($n=123$) who delivered at UNC Women's Hospital between January 2000 and February 2010 and had second trimester genetic screening performed. Using banked frozen serum matched by age, race, BMI, parity, season of blood draw, and gestational age at serum collection, we measured levels of 25(OH)D, VEGF, soluble fms-like tyrosine kinase-1 (sFLT-1), and placental growth factor (PlGF). We used non-parametric ROC analysis to compare predictive values of 25(OH)D and angiogenic factors.

RESULTS: Women who later developed severe preeclampsia had significantly lower levels of both VEGF and 25(OH)D in early pregnancy compared to controls (1.6 pg/ml vs 3.2 pg/ml, $p<0.001$; 75.1 nmol/l vs 106.6 nmol/l, $p<0.001$, respectively). We found no correlation between 25(OH)D and VEGF levels ($r_{pearson} = 0.01$, $p=0.87$). 25(OH)D level alone was equivalent as a predictive marker for severe preeclampsia compared to VEGF and sFLT-1/PlGF ratio. A composite of both 25(OH)D levels and sFLT-1/PlGF ratio was more predictive than either alone (AUC 0.78 vs 0.72 and 0.60, respectively).

CONCLUSIONS: Combining circulating levels of 25(OH)D with sFLT-1/PlGF ratio predicts severe preeclampsia better than either marker alone.

38 Prevention of group B streptococcus (GBS) colonization by multiple GBS serotypes using a novel GBS vaccine

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OBJECTIVE: Using a murine model, our objective is to optimize various formulations of our novel, univalent GBS vaccine and determine if they safely promote short and long term immunity and prevent vaginal colonization to multiple GBS serotypes.

STUDY DESIGN: C5a peptidase, a surface protein found on multiple serotypes of GBS, was microencapsulated in Poly lactide-co-glycolide acid (PLGA) using a water in oil in water double emulsion technique. 6-8 week old female ICR mice were vaccinated with 5 different formulations of vaccine: free C5a antigen, PLGA 72:25 0ug, PLGA 75:25 10ug, PLGA 75:25 30ug, and PLGA 50:50 30ug. Vaccines were admin-

istered either intramuscular (IM) or intranasal (IN). Mice were given booster doses of the same formulation and the same route of administration at 4 and 8 weeks. Serial serum and vaginal washings were obtained at weeks 4, 8, 11, 15, and 27 to determine antibody response. C5a specific IgG and IgA antibody responses were determined by colormetric ELISA. Mice were also challenged vaginally with GBS serotypes Ia, III, and V. After 24 hours, vaginal swabs were obtained, grown on blood agar plates, and number of GBS colonies were counted.

RESULTS: Of the various formulations and routes of delivery tested, both PLGA 75:25 30ug and 50:50 30ug IM and IN vaccines elicited a significant systemic IgG immune response with highest titers attained of 1:100,000. IgA immune responses were observed, but were inconsistent. For the vaginal colonization studies, mice vaccinated with PLGA 50:50 30ug and 75:25 30ug via the IM route showed no vaginal colonization with serotypes Ia and III. For GBS serotype V, less protective immunity was observed.

CONCLUSIONS: In the murine model, IM and IN administration of PLGA 50:50 30ug and 75:25 30ug vaccine formulations rendered a strong systemic immune response and prevented GBS colonization of the vaginal vault by serotypes Ia and III. Differences in protection to colonization by serotype V may be explained by differential C5a peptidase expression.

39 Pravastatin upregulates eNOS activity in the sFLT-1 mouse model of preeclampsia

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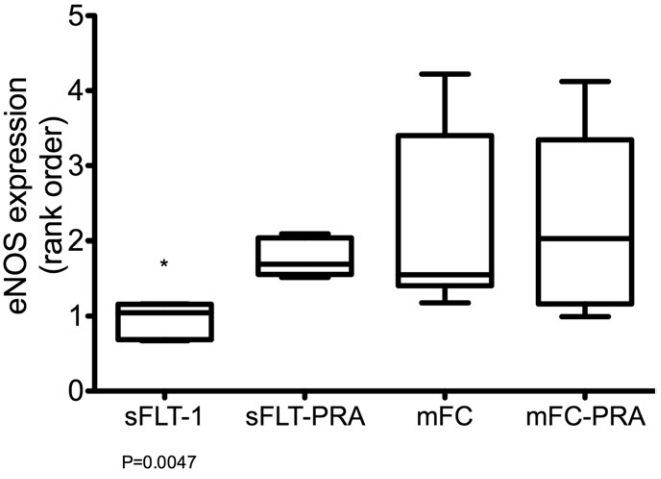
OBJECTIVE: We have previously shown that pravastatin administered to a well-characterized mouse model of preeclampsia decreases the production of the antiangiogenic sFlt-1 and prevents the associated vascular dysregulation. Endothelial nitric oxide synthase (eNOS) is the enzyme responsible for the production of nitric oxide, one of the most potent vascular smooth muscle relaxants. We hypothesize that pravastatin's action is mediated through eNOS, rather than cholesterol reduction or upregulation of mebrane bound vascular endothelial growth receptor-1 (VEGFR-1).

STUDY DESIGN: At day 8 of gestation, CD-1 mice were randomly allocated to injection of 10^9 PFU of the adenovirus carrying sFlt-1 or mFc control via the tail vein, and to receive pravastatin (Pra; 5 mg/kg/day) dissolved in drinking water or control. This resulted in 4 groups: sFlt, sFlt-Pra, mFc and mFc-Pra. Baseline and day 18 sera were collected. On day 18, dams were sacrificed and their aorta and kidneys collected and homogenized for western blot analysis for eNOS protein expression in the aorta and VEGFR1 expression in the kidneys. Western blot protein levels were normalized to actin. Serum cholesterol levels were determined using ELISA. Kruksal-Wallis with Dunn's post-hoc test was performed (statistical significance: $P<0.05$).

RESULTS: Pravastatin treatment in the sFlt group up-regulated eNOS expression by 60%, to levels similar to control mice ($P=0.005$; Figure). Cholesterol levels were not significantly different between groups, despite a trend toward lower levels with pravastatin administration. Renal VEGFR-1 levels were similar across groups.

CONCLUSIONS: Pravastatin administration prior to the onset of preeclampsia prevents the associated vascular dysfunction through pleiotropic effects by upregulating eNOS expression in the vasculature in the mouse model. This supports a role for statins in preventing the vascular abnormalities of preeclampsia.



40 Utility of an intrapartum rapid group B streptococcus test

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OBJECTIVE: Group B streptococcus (GBS) early-onset sepsis is a leading cause of neonatal morbidity and mortality. Two-thirds of infants with GBS sepsis are born to mothers with a negative third-trimester GBS culture—the current screening test. Given the transient nature of GBS colonization we evaluated the test characteristics of a rapid intrapartum GBS test and the current screening test along with the incidence of GBS conversion from the third trimester to intrapartum.

STUDY DESIGN: Women presenting to labor and delivery with an antepartum GBS culture were enrolled. Intrapartum recto-vaginal samples were obtained per CDC guidelines for the culture and rapid test. The intrapartum culture was the gold standard to calculate test characteristics and 95% confidence intervals.

RESULTS: Among 559 women who delivered 563 neonates, GBS prevalence was 19.5% with antepartum culture and 23.8% with intrapartum culture. Compared with intrapartum culture, antepartum culture had sensitivity of 69.2% (60.6-76.9) and specificity of 96.0% (93.7–97.7). The rapid intrapartum test showed sensitivity of 90.8% (84.6–95.2), specificity of 97.6% (95.7–98.9), positive predictive value of 92.3% (86.2–96.2) and negative predictive value of 97.2% (95.1–98.5). The incidence of GBS conversion from the late third trimester to labor was 10.4%. The time interval between the antepartum and intrapartum tests was the same for women who did not convert as for those who converted ($P=0.99$). Compared with women who identified as Caucasian, African-American ($P=0.02$) and Hispanic ($P=0.02$) women were significantly more likely to convert. The incidence of neonatal blood culture was 35% among women who converted to negative versus 17% among women who remained negative.

CONCLUSIONS: This intrapartum rapid GBS test has excellent test characteristics and may be superior to the antepartum culture for accurately detecting intrapartum GBS colonization. Use of this rapid intrapartum test may improve the precision of neonatal sepsis evaluations, and may thus impact the incidence of neonatal GBS sepsis.