ORAL PLENARY SESSION II

(Fellows Plenary)

Friday, January 22, 1999
8:00 am - 10:00 am

Moderators:	**Donald R. Coustan, MD**
	J. Peter VanDorsten, MD
Judges:	**Sharon L. Dooley, MD**
	Kenneth Leveno, MD
	Mary Jo O'Sullivan, MD

Continental Ballroom 4-6
Abstract Numbers 29-36

29 THE ROLE OF EXTRACELLULAR SUPEROXIDE DISMUTASE (ECSOD) IN HUMAN PREGNANCY. KA Boggess, *HH Kay, JD Crapo, WNP Herbert, TD Oury.*Depts of Ob/Gyn, Med, Path Duke University Medical Center Durham, NC.

OBJECTIVES: Nitric oxide (NO) may be involved in the maintenance of both low placental vascular tone and uterine quiescence during pregnancy. ECSOD has been identified as a major regulator of NO bioavailability within the lung, and its expression within both murine uterus and placenta has been reported. We sought to characterize ECSOD localization and activity in labored and unlabored myometrium, in placentas through healthy pregnancy, and at the site of placental implantation.

STUDY DESIGN: First and second trimester villi were obtained at pregnancy termination; third trimester placental samples were taken at delivery. Lower uterine segment and placental implantation site biopsies were obtained at the time of c/s. After separation from cellular SOD, ECSOD activity was measured by inhibition of cytochrome *c* reduction. ECSOD protein localization was performed using indirect immunoperoxidase, and mRNA localization was determined by in-situ hybridization.

RESULTS: ECSOD activity was similar in villi from all trimesters, though localization varied. Within third trimester placentae, ECSOD localized to the vascular smooth muscle within the villous extracellular space, as expected; however ECSOD was found intracellularly within first and early second trimester trophoblasts. ECSOD activity was similar between labored and unlabored myometrium and localized to the extracellular matrix. At the placental implantation site, ECSOD was intracellular, within intermediate trophoblasts. In-situ hybridization confirmed ECSOD mRNA within the intermediate trophoblasts.

CONCLUSIONS: ECSOD is present in the human placenta, uterus, and at the site of placental implantation. Intracellular ECSOD within intermediate, first and second trimester trophoblasts suggests a role for ECSOD at the site of implantation and during fetal vessel formation. That ECSOD activity is similar between labored and unlabored myometrium suggests that other mechanisms may regulate uterine NO bioavailability.

30 COX-2 ACTIVITY MEDIATES INFLAMMATORY PRE-TERM LABOR IN THE MOUSE. *G. Gross*[X], T. Imamura[X], S. Vogt[X], D.M. Nelson, Y. Sadovsky, L. Muglia[X] Depts. Of OB/GYN and Pediatrics, Washington University, St. Louis, MO

OBJECTIVE: To test whether selective inhibition of either cyclooxygenase (COX)-1 or -2, the enzymes responsible for the first committed step in prostaglandin (PG) biosynthesis, can potentially result in therapeutic, but not toxic, effects of pharmacologic tocolysis.

STUDY DESIGN: Mice at day 14.5 gestation were treated with lipopolysaccharide (LPS) to reliably promote preterm labor (PTL) and assess the contributions of COX-1 and -2 in pharmacologic and genetic studies. Specific inhibitors of COX-1 (Resveratrol) and -2 (NS-398) activity were compared to the non-selective inhibitor indomethacin. Genetically altered mice deficient in COX-1 activity were also assessed. Parturition phenotypes of all animals were studied. Uterine and ovarian tissues from all study groups were analyzed for both COX-1 and -2 mRNA as well as local tissue prostaglandin (PG) concentration.

RESULTS: All animals receiving LPS delivered within 24 hours. A dose-dependent reduction in PTL was seen with increasing indomethacin doses, such that 10 mg/kg/d prevented delivery in 80% of mice. In contrast mice treatment with Resveratrol or NS-398 alone and in combination failed to show significant attenuation of PTL. Mice deficient in COX-1 activity all delivered following LPS administration. Northern analysis of uterus and ovary from wild type mice demonstrated marked induction of COX-2 mRNA two hours following LPS with return to baseline at eight hours, while no change in COX-1 mRNA activity was seen. Levels of PGF2a increased at 2 hours with return to basal levels at 8 hours. Indomethacin completely suppressed PGF2a production, while the specific inhibitors only partially attenuated production.

CONCLUSIONS: Combined pharmacologic inhibition of COX with near total ablation of PG production effectively attenuates LPS-mediated PTL in the mouse. The absence of COX-1 activity does not preclude the occurrence of PTL. COX-2, rather than COX-1 mRNA is induced in inflammatory PTL in the mouse suggesting that development of more effective COX-2 inhibitors could effect successful tocolysis with reduced fetal side effects.

31 A PROSPECTIVE RANDOMIZED DOUBLE-BLIND TRIAL OF ORAL NIFEDIPINE AND INTRAVENOUS LABETALOL IN HYPERTENSIVE EMERGENCIES. *S. Vermillion*[x], J. Scardo, R. Newman, S. Chauhan. Department of Ob/Gyn, Medical University of SC, Charleston, SC.

OBJECTIVE: To compare the efficacy of oral nifedipine and IV labetalol in the acute management of hypertensive emergencies of pregnancy (HEP).

STUDY DESIGN: We performed a prospective randomized double-blind comparison of oral nifedipine (10 mg) and IV labetalol (20 mg) in 50 peripartum patients with sustained systolic blood pressure (SBP) >170 mmHg or diastolic blood pressure (DBP) >110 mmHg. Both agents were repeated at sequentially escalating dosages every 20 minutes until a therapeutic goal of SBP <160 mmHg and DBP <100 mmHg was achieved. Crossover occurred if the treatment goal was not achieved after 5 doses. Primary outcome was time to achievement of the therapeutic goal. Secondary outcome variables were agent failure rate, change in SBP/DBP over time, urinary output, and adverse effects. Data were analyzed by unpaired t-test, Mann-Whitney U-test, and ANOVA for repeated measures with Bonferroni multiple comparison post-test analysis.

RESULTS: Mean time to achieve BP goal was significantly shorter with nifedipine, 25±13.6 ($\bar{X}$±SD), than with labetalol 43.6±25.4 minutes ($p=0.002$). No patients required crossover therapy. Both agents demonstrated a significant decrease in enrollment SBP and DBP within 15 minutes. Urine output was significantly increased ($p<0.001$) at one hour after nifedipine (99±99 cc) ($\bar{X}$ ±SD) compared to labetalol (44.8±19.1 cc) and remained significantly increased at 2, 6, 12, 18, and 24 hours after initial administration. Adverse effects were rare. There were no significant differences in maternal age, gestational age, number of antepartum patients, and enrollment blood pressures between groups.

CONCLUSIONS: Both oral nifedipine and IV labetalol are effective in the acute management of HEP; however, nifedipine controls hypertension more rapidly and is associated with a significant increase in urinary output.

32 INTERGENERATIONAL PATERNAL PREDISPOSITION TO PREECLAMPSIA *Esplin MS*[*], Fraser A[*], Kerber R[*], Mineau G[*], Carillo J[*], Varner M. Dept. Of Ob/Gyn, Univ. Of Utah School of Medicine, SLC, Ut.

OBJECTIVE: Recent evidence suggests that certain fetal genotypes may predispose to the development of preeclampsia. Our purpose was to determine if preeclampsia is more common in pregnancies fathered by males who were themselves delivered of pregnancies complicated by preeclampsia.

METHODS: Using the Utah Population Database, a multi-generational linked database, we identified 1,900 males born of a pregnancy complicated by preeclampsia between the years 1947 to 1957. Each case was reviewed and the diagnosis was confirmed by one of the authors. Of these cases, 298 were linked to at least one birth certificate of their offspring born between 1970 and 1992. There were 947 offspring identified. Each case was randomly matched to two controls (pregnancies delivered of viable male infants not complicated by preeclampsia who also subsequently had at least one pregnancy in the database) by maternal age, birth year and birth order. The 596 control males identified were then linked to 1,950 offspring. Pregnancy outcomes for all case and control offspring were evaluated by review of birth certificate records and ICD 9 codes. Any case with a preexisting maternal medical condition or complication of pregnancy (i.e. chronic hypertension, diabetes or multiple gestation) was excluded. Odds ratios for the development of preeclampsia in the offspring pregnancy were calculated using stepwise logistic regression including evaluation of 15 possible confounding variables. After elimination of co-variates, a model was constructed to adjust for the three most likely confounding variables.

RESULTS: There were 26 pregnancies complicated by preeclampsia among the 947 (2.74%) cases compared to 26 pregnancies of the 1,950 (1.33%) controls. The crude odds ratio was 2.09 (95% CI 1.17-3.74) for the development of preeclampsia in the study group. When these results are adjusted using stepwise logistic regression controlling for birth year, previous live births and birth weight, the study group had an odds ratio of 2.12 (95% CI 1.17 - 3.84).

CONCLUSION: Men who were the product of a pregnancy complicated by preeclampsia were significantly more likely than controls to father a pregnancy complicated by preeclampsia. These findings support the theory that fetal genotype plays a role in the development of preeclampsia. Future attempts to delineate the pathophysiology of preeclampsia should consider paternal and fetal contributions.

33 A RANDOMIZED TRIAL OF CONJUGATED IA GROUP B STREPTOCOCCAL VACCINE IN A RABBIT MODEL OF ASCENDING INFECTION. *JK Davies*, S Lee, J Eskens, S Woodcock, RS McDuffie, LC Paoletti, RS Gibbs. Dept. of Ob/Gyn, Univ. of Colorado, Denver, CO and Dept. of Medicine, Channing Laboratory, Boston, MA.

OBJECTIVE: Maternal vaccination may become a central strategy in the prevention of early onset neonatal Group B streptococcal (GBS) sepsis. Unlike earlier GBS polysaccharide vaccines which were poorly immunogenic, the newer GBS vaccine has been conjugated to tetanus toxoid (TT) and is significantly more immunogenic. We sought to evaluate a vaccine conjugated to tetanus toxoid using our rabbit model of ascending infection.

STUDY DESIGN: Rabbit does were randomly assigned to receive either GBS type Ia (Ia-TT) or control, GBS type III (III-TT) vaccine. Does were vaccinated 7 days prior to conception, and 7 and 21 days after conception. Does were mated on three successive days. On days 28-30 (of 30 day gestation), does were endoscopically inoculated intracervically with 10^6 cfu type Ia GBS. Labor was induced if does were undelivered after 72 hours. Does were observed for ≤ 7 d. Pups were observed for ≤ 96 h. We obtained maternal cultures from uterus, peritoneum, and blood and neonatal cultures from mouth, anus and blood. Serum antibody levels were also obtained. Assuming a 90% reduction in incidence of infection in vaccinated animals, 14 animals per arm would be needed to demonstrate statistical significance.

RESULTS: Pup survival was significantly better in the group receiving Ia-TT (p=0.047). Several other outcomes of interest, although not reaching statistical significance, showed a trend towards improved outcomes in the Ia-TT group.

Outcome	Ia-TT	III-TT	Pvalue
Does with fever	8 / 9 (88.8%)	10 / 12 (83.3%)	NS
Does with + uterine culture	6 / 9 (66.7%)	9 / 12 (75.0%)	NS
Does with + blood culture	0 / 9	2 / 12 (16.7%)	NS
Does with severe illness	0 / 9	4 / 12 (33.3%)	NS
Liveborn pups	49 / 83 (59.0%)	38 / 97 (39.2%)	0.047
Pups + oral-anal culture	59 / 77 (76.6%)	77 / 91 (84.6%)	NS
Pups + blood culture	34 / 76 (44.7%)	43 / 89 (48.3%)	NS

CONCLUSIONS: This is the first study to evaluate conjugated GBS vaccine using a model of ascending infection. Although Ia-TT vaccine led to improved survival, the vaccine fell short of its expected efficacy with respect to prevention of GBS disease under our experimental conditions. Supported in part by NIH Contract # A1 25152.

34 THROMBIN, A NON-CLASSIC UTEROTONIC AGONIST THAT PRODUCES PHASIC MYOMETRIAL CONTRACTIONS Elovitz M[x], *Saunders T[x], Phillippe M. Section of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, University of Chicago, Chicago, IL.*

OBJECTIVE: Although well described clinically, the mechanisms underlying the generation of phasic myometrial contraction in response to abrutio placentae are poorly understood. Our studies were performed to test the hypothesis that thrombin, a factor produced during activation of the coagulation cascade, can activate the phosphatidylinositol (PI-)signaling pathway resulting in the generation of phasic myometrial contractions.

STUDY DESIGN: Myometrial tissue was obtained from proestrus/estrus Sprague-Dawley rats. *In vitro* contraction studies were performed using thrombin with and without 2-nitro-4-carboxyphenyl-N,N-diphenylcarbamate (NCDC, a PLC inhibitor), thimerosal (THIM, an inositol triphosphate receptor inhibitor), ruthenium red (RRED, a ryanodine receptor inhibitor), and phorbol dibutyrate (PDB, a protein kinase C activator).

RESULTS: Thrombin (1-100 U/mL) stimulated a dose-related increase in phasic contractions comparable in character to those produced in response to oxytocin. The thrombin-stimulated phasic contractions were markedly suppressed in response to NCDC, THIM, and RRED, thereby confirming the importance of the PI-signaling pathway during these events. Consistent with the effects of PDB on oxytocin-stimulated contractions, PDB had an inhibitory effect on thrombin-stimulated contractile activity.

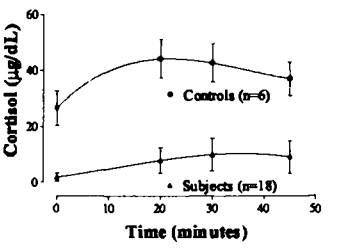
CONCLUSIONS: Thrombin is known to bind to a G-protein coupled receptor; however previous reports have suggested that the effects of thrombin on smooth muscle contractile activity are mediated by activation of tyrosine kinases. Our studies to date have been unable to confirm an effect of genestein or herbimycin A (two tyrosine kinase inhibitors) on thrombin-stimulated contractions; therefore, it is yet to be determined whether the thrombin effect is mediated by Gq/phospholipase C-β or tyrosine kinase/phospholipase C-γ related mechanisms. (Funded by NIH HD28506 and HD32449)

35 THE EFFECTS OF REPEATED DOSES OF ANTENATAL CORTIOCOSTERIODS ON MATERNAL ADRENAL FUNCTION. *DS McKenna*, GM Wittber,[x] P Samuels. Department of Obstetrics and Gynecology, The Ohio State University, Columbus, OH.

OBJECTIVE: To determine if multiple courses of maternal antenatal steroids given to enhance fetal lung maturity result in suppression of the maternal pituitary-adrenal axis.

STUDY DESIGN: The standard low dose adrenocorticotrophic hormone (ACTH) stimulation test (0.5 μg intravenous), a very sensitive test for adrenal insufficiency, was administered to 18 pregnant women (mean gestational age 30.2 weeks) who had received at least 2 weekly courses of antenatal betamethasone and also to 6 pregnant controls (mean gestational age of 31.4 weeks) who had not received steroids. The baseline levels and kinetics of maternal serum cortisol /in μg/mL) were compared between the two groups.

RESULTS: Mean baseline cortisol was significantly depressed in women who received betamethasone compared to controls (1.9±1.5 vs 26.5±6.2; P<0.001). At each time point after ACTH stimulation, mean cortisol was again significantly lower in women who had received betamethasone (P<0.001). The time to peak cortisol level was significantly delayed in women who had received betamethasone compared to controls (35±1.6 vs. 21.7±2.7 minutes; P<0.001).



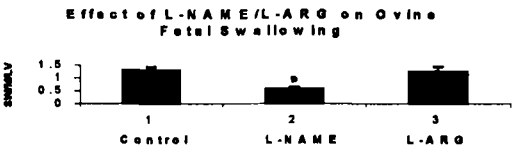
CONCLUSION: The administration of multiple courses of antenatal betamethasone results in barely detectable maternal serum cortisol levels and a diminished response to aCTH stimulation, indicative of decreased steroid stores and adrenal cortical atrophy. This has potentially serious maternal ramifications. Repeated courses of antenatal steroids have not been shown to increase efficacy over a single course in accelerating fetal lung maturity and should be reserved for those women who are at the highest risk for preterm delivery.

36 NITRIC OXIDE MODULATION OF OVINE FETAL SWALLOWING. *MA El-Haddad[x]*, MJ Nijland[x], S Ma[x], MG Ross. Dept Ob/Gyn, Harbor-UCLA Med Ctr, Torrance, CA.

OBJECTIVE: Human and ovine fetuses demonstrate an enhanced rate of swallowing, an activity critical for gastrointestinal development and amniotic fluid regulation. Fetal swallowing may be modulated by both systemic and central factors. Nitric oxide (NO) is a central neuromodulator and NO synthase has been localized to brain regions regulating thirst and swallowing. We sought to determine if NO contributes to the regulation of spontaneous ovine fetal swallowing.

STUDY DESIGN: Six time-dated pregnant ewes with singleton fetuses (129±1 d) were chronically prepared with fetal vascular and lateral ventricle (LV) catheters, and electrocorticogram (ECoG) and esophageal electromyogram electrodes. Following a 2 h control period, fetuses were monitored following LV injection of L-NAME (NO synthase inhibitor). Following 2 h, fetuses received an LV injection of L-Arginine (NO precursor; to reverse effects of L-NAME). All fetuses received an additional control study of fetal swallowing prior to and following LV injection of artificial cerebrospinal fluid (aCSF). Fetal swallowing, blood pressure and heart rate were monitored continuously and blood samples drawn at timed intervals. Data were analyzed with repeated measures ANOVA and paired t-test as appropriate (p<0.05).

RESULTS: Suppression of central NO with L-NAME injection significantly reduced mean (±SEM) spontaneous fetal swallowing (1.27±0.1 to 0.56±0.1 swallow,/min low voltage ECoG; p=0.001). Restoration of central NO by L- Arginine injection significantly increased fetal swallowing to pre-L-NAME levels (1.24±0.2 swallows/min low voltage). There were no changes in fetal ECoG activity, blood pressure, plasma osmolality or electrolytes during the study. Fetal swallowing did not change during the control study of aCSF injection.



CONCLUSIONS: NO is an important neuromodulator of fetal swallowing activity. Elevated fetal central NO synthase activity may contribute to the marked levels of fetal swallowing and the regulation of amniotic fluid volume.