HYPERTENSION/PHYSIOLOGY

Abstracts 18 – 26

Moderators: George Saade, MD; Hal Lawrence, MD, 2010 Honorary Member

18 Effect of continuous infusion of vascular endothelial growth factor on blood pressure in a mouse model of preeclampsia induced by SFLT-1 overexpression

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OBJECTIVE: Inhibition of vascular endothelial growth factor (VEGF) by soluble fms-like tyrosine kinase1 (sFlt-1) plays a role in the pathogenesis of preeclampsia. Our objective was to determine the effect of recombinant human VEGF-121 on blood pressure (BP) in a mouse model of preeclampsia induced by sFlt-1 overexpression.

STUDY DESIGN: CD-1 pregnant mice at day 8 of gestation were randomly allocated to subcutaneous insertion of osmotic minipump prepared with either VEGF-121 or phosphate buffered-saline solution (PBS) as a solvent-control. Pumps were calibrated to continuously deliver 400 μg/kg/day or equivalent PBS for 10 days. Telemetric BP catheters were inserted through the left carotid artery into the aortic arch. BP was recorded continuously in the conscious unrestrained mice for 10 days. At day 9 of gestation, mice were injected through the tail vein with adenovirus vector carrying sFlt-1 (10^9 PFU). Animals were sacrificed on day 18 of gestation. Pups and placenta were weighted. Student t-test was used for statistical analysis (significance: $p<0.05$).

RESULTS: BP did not differ significantly between the two groups on days 8 and 9 of gestation. From day 10 to day 18 of gestation, systolic, diastolic and mean BPs were significantly lower in the VEGF-121 treated group compared with the control group. The drop in mean BP ranged between 16.15 to 26.33 mmHg during the treatment period, with the greatest drop occurring on day 12 of gestation (103.08 $\pm$ 5.30 vs 76.74 $\pm$ 2.95 mmHg). Placenta mean weight was not significantly different between the two groups, but mean pup weight was significantly lower in the control group as compared with the VEGF-121 group (1.01 $\pm$ 0.09 vs 1.30 $\pm$ 0.24 g; $P<0.05$).

CONCLUSION: Continuous VEGF-121 therapy ameliorates the hypertension and pup growth abnormality in this mouse model of preeclampsia. This finding underscores the role of VEGF in gestational vascular adaptations, and of sFlt-1 as one of the factors involved in the pathogenesis of preeclampsia. Use of VEGF for the treatment of preeclampsia may be worthy of a trial.

0002-9378/$ – see front matter • doi:10.1016/j.ajog.2009.10.050

19 Maternal and fetal effects of bay 41-2272, a direct soluble guanylate cyclase activator, in a model of preeclampsia and intra uterine growth restriction

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OBJECTIVE: Preeclampsia and intra uterine growth restriction (IUGR) are strongly associated with reduced uterine perfusion and abnormal placentation. Increased production of nitric oxide (NO) by the endothelium contributes to the hemodynamic changes associated with normal pregnancy. Conversely, a reduction in NO production has been observed in preeclampsia and IUGR. BAY 41-2272 (BAY) is a novel NO-independent direct activator of soluble guanylate cyclase (sGC) that causes vasodilation in systemic and local circulations. However, BAY has not been studied during the pregnancy. We hypothesized that BAY may reduce maternal blood pressure and improve fetal growth in an animal model of preeclampsia and IUGR.

STUDY DESIGN: To test this hypothesis, we studied the effects of BAY in pregnant rats after NO synthase inhibition with N(omega)-Nitro-L-arginine methyl ester (LNAME). Osmotic minipumps were inserted subcutaneously into timed pregnant wistar-han rats on day 17 of pregnancy. The pumps were loaded to continuously deliver either vehicle or LNAME 50 mg/d, either alone or with BAY 1mg/kg/d. Maternal arterial pressure and uterine resistance index were measured at 16 and 20 days. A c-section was performed on day 21. Pup weight and length, litter size and placental weight were recorded.

RESULTS: Compared to control animals, pregnant rast with chronic NO synthase inhibition had increased arterial blood pressure, reduced pup weight and length and decreased placental weight. In comparison with LNAME-treated rats, BAY attenuated maternal arterial blood pressure (138$\pm$2.5 vs 120$\pm$2.1 for systolic pressure and 100$\pm$1.9 vs. 95$\pm$2.1 for diastolic pressure; $p<0.05$) and improved pup weight (3.67$\pm$0.11g vs 4.42$\pm$0.06 g; $p<0.01$) and length (3.55$\pm$0.05cm vs 3.88$\pm$0.03cm; $p<0.01$). In addition, placental weight was increased in BAY + LNAME group vs. LNAME alone (0.55$\pm$0.03g vs 0.49$\pm$0.02g; $p<0.01$).

CONCLUSION: We concluded that BAY reverses the maternal and fetal effects of LNAME-induced placental insufficiency in pregnant rats. We speculate that BAY may provide a novel treatment for preeclampsia and/or IUGR.

0002-9378/$ – see front matter • doi:10.1016/j.ajog.2009.10.051

20 Assessment of global protein misfolding load by urine "Congo Red Dot" test for diagnosis and prediction of outcome in women with preeclampsia (PE)

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OBJECTIVE: PE is characterized by increased excretion of misfolded proteins with affinity for Congo Red (CR), an azo dye used to detect aberrant brain amyloidal aggregates in Alzheimer's and prion disease. We sought to design and validate a diagnostic and prognostic test for PE based on urine congophilia as a measure of global protein misfolding load in pregnancy.

STUDY DESIGN: 347 pregnant women were enrolled prospectively in the following groups: normotensive controls (CRL n=98, GA:27[7-42w]); chronic hypertension (crHTN n=40, GA:32[11-41w]), gestational hypertension (gHTN n=8 GA:37[26-39w]), mild PE (mPE n=36, GA:36[24-41w]), severe PE (sPE n=117, GA:32[22-42w]), superimposed PE (spPE n=33 GA:33[18-40w]). 35 asymptomatic women were tested serially throughout gestation. A "CR Dot" test was standardized with equal urine protein and objectively quantified within minutes as %CR retention (CRR). CRR was evaluated for its ability to predict an indicated delivery for PE (IND) compared to protein-to-creatinine ratio (P/C) and the previously validated urine sFlt1/PlGF ratio.

RESULTS: 61% (211/347) of women had IND: CRL: 4%; crHTN: 40%; gHTN: 75%; mPE: 69%; sPE: 99%; spPE: 100%. 77% (162/211) of