

## **2008 Vision Grant: Interim Progress Report**

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I would like to thank the Preeclampsia Foundation for awarding my research proposal, “Cerebral vessel reactivity and blood-brain barrier changes with exposure to plasma from preeclamptic women” a 2008 Vision Grant. Since that time, we have performed experiments evaluating both reactivity of cerebral arteries and permeability of cerebral veins exposed to human plasma from normal nonpregnant, normal pregnant and preeclamptic women. Two main studies have been established under our research proposal. The first, entitled “Resistance Artery Adaptation to Pregnancy Counteracts the Vasoconstricting Influence of Plasma from Normal Pregnant Women” has been completed. This study examined the effect of perfusing plasma from healthy nonpregnant and normal pregnant women on cerebral arteries from nonpregnant and late pregnant rats to examine if and how circulating factors in the plasma of pregnant women change the function of these brain vessels. This work was presented as a poster at the Society of Gynecologic Investigation meeting in Glasgow, Scotland in 2009 and was published in the abstract proceedings in *Reproductive Sciences*. The reference for this abstract is: Amburgey OA, Reeves SA, Bernstein IM, Cipolla MJ. Plasma from Normal Pregnant Women Diminishes Endothelium-Derived Hyperpolarizing Factor (EDHF) Production in Cerebral Arteries. *Reproductive Sciences*. 2009; 16 (3 Supplement): 263A. A copy of the abstract is found at the end of this progress report. In addition, a manuscript has been completed and submitted for publication in *Reproductive Sciences*.

The second study established under our research proposal is entitled “Changes in Cerebral Artery Function and Cerebral Vein Permeability with Exposure to Preeclamptic Plasma.” One group of experiments compared how cerebral artery reactivity and endothelial vasodilator production changed in brain vessels from pregnant rats when these vessels were exposed to plasma from normal pregnant women vs. preeclamptic women. We then evaluated if the brain vessels adapted to hypertension, and tested plasma from preeclamptic women in both cerebral vessels from normal pregnant rats as well as rats that were made hypertensive in an effort to model and mimic preeclampsia. In order to evaluate the effect of circulating factors in the plasma of preeclamptic women on blood-brain barrier function, we performed experiments testing permeability of cerebral veins from normal pregnant rats and hypertensive rats exposed to plasma from normal pregnant women as well as preeclamptic women. These experiments have been completed, and data analysis is ongoing. We hope to present this work at a national conference next year and plan on submitting a manuscript in the next few months.

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### **Plasma from Normal Pregnant Women Diminishes Endothelium-Derived Hyperpolarizing Factor (EDHF) Production in Cerebral Arteries**

**Background:** Circulating factors during pregnancy can have significant effects on endothelium, altering vascular resistance to promote either normal or pathologic adaptation. We investigated the effect of circulating factors during pregnancy on endothelial vasodilator production and myogenic tone of the posterior cerebral artery (PCA) by perfusing with plasma from nonpregnant (NP) and normal pregnant (P) women.

**Materials and Methods:** Third-order branches of PCAs from virgin SD rats were dissected, mounted in an arteriograph chamber, and perfused with plasma (20% in buffer) pooled from nonpregnant (n=6) or normal, non-laboring pregnant women (n=6; mean GA 33.8±0.6 wks). Lumen diameter and myogenic tone were measured in response to

intravascular pressure (25-150 mmHg), after which the nitric oxide (NO) synthase inhibitor L-NNA (0.1 mM) and the cyclooxygenase (COX) inhibitor indomethacin ( $10^{-5}$  mM) were added to the bath. Changes in diameter were used as a measure of basal NO and prostacyclin production, respectively. In the presence of NOS/COX inhibition, calcium ionophore A23187 was cumulatively added to the bath to measure EDHF response.

**Results:** Both NP and P groups developed myogenic tone at 50mmHg that was maintained at 150mmHg; however, the P group developed greater tone at 100, 125, and 150mmHg:  $33\pm 1$  vs.  $40\pm 2\%$ ,  $32\pm 1$  vs.  $42\pm 3\%$ ,  $33\pm 1$  vs.  $42\pm 1\%$ , (all  $p < 0.01$ , NP vs. P). Vessels from both groups constricted similarly in response to L-NNA ( $30\pm 4$  vs.  $28\pm 4\%$ , n.s.) and had minimal response to indomethacin. Addition of A23187 in the presence of NOS/COX inhibition caused dilation in both groups of vessels; however, the EDHF dilation was diminished in PCAs exposed to pregnant plasma [Figure 1]. The percent dilation to  $1.0\mu\text{M}$  A23187 in PCAs perfused with NP vs. P plasma was  $111\pm 17$  vs.  $35\pm 11\%$ ;  $p < 0.01$ .

**Conclusions:** These results suggest that circulating factors during pregnancy affect the cerebral endothelium to diminish EDHF and increase tone, an effect that may impact cerebrovascular resistance and control of blood flow in the maternal brain.