48 FETAL PROGRAMMING OF ADULT BLOOD PRESSURE IN A MOUSE MODEL OF ADVERSE UTERINE ENVIRONMENT INDUCED BY NITRIC OXIDE SYNTHASE 3 (NOS3) DEFICIENCY: EFFECT OF POSTNATAL STRESS

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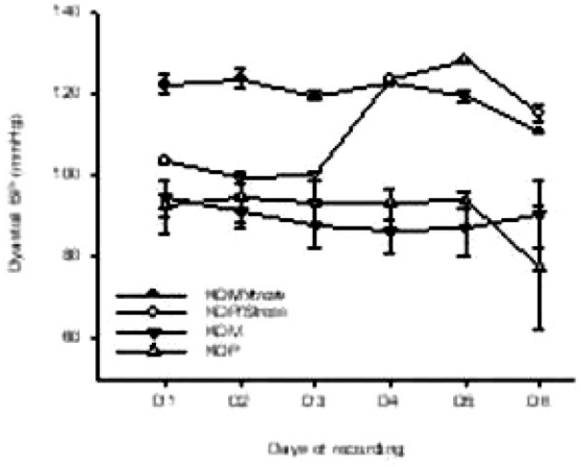
OBJECTIVE: Nitric oxide and NOS3 are critical in the regulation of utero-placental perfusion. We have previously shown that heterozygous mice offspring born to transgenic mothers lacking NOS3 have systolic hypertension in later life compared to offspring born to wild type mothers. Our objective was to determine whether the cardiovascular response to stress is also altered in this animal model of fetal programming.

STUDY DESIGN: NOS3 knockout and wild type mice were cross-bred to obtain maternally-derived (KOM) and paternally-derived (KOP) heterozygous offspring. At 14 weeks of age, blood pressure (BP) catheters were inserted through the left carotid artery into the aortic arch. BP was recorded continuously for 6 days by telemetry in the conscious unrestrained offspring. Stress was induced by placing the mice in a caging system attached to a shaking platform that provided intermittent shaking between the 3rd and 4th day of recording. Mean BP (MBP), pulse pressure (PP), systolic BP (SBP) and diastolic BP (DBP) were analyzed. Student t-test was used for statistical analysis (significance: $p<0.05$).

RESULTS: As previously reported without stress, KOM mice offspring had significantly higher MBP and PP compared with KOP. This difference was accentuated following stress. Compared with KOP, DBP in KOM before stress was not significantly different, but became significantly higher after stress (Figure).



Diastolic Blood Pressure

CONCLUSION: The adverse uterine environment in the NOS3 knockout mice leads to systolic hypertension in the adult offspring, which is further compounded by diastolic hypertension in response to postnatal stress.

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49 CONTINUOUS INFUSION WITH WITH 17-HYDROXYPROGESTERONE CAPROATE (17-P) INTO THE FETAL OR MATERNAL ARTERIAL CIRCUITS OF THE EX VIVO PLACENTAL COTYLEDON MODEL ATTENUATES VASOCONSTRICTION BY THROMBOXANE AND ANGIOTENSIN-II

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OBJECTIVE: Weekly injections of 17-Hydroxyprogesterone Caproate (17-P) has been shown to reduce the recurrence rate of preterm deliveries. Our prior research has shown that bolus injections of 17-P into the fetal-placental arteries reversed vasoconstriction caused by the continuous infusion of thromboxane. Our objectives were to determine if a continuous infusion of 17-P into the fetal-placental arteries would attenuate the vaso-active effects of bolus doses of thromboxane and angiotensin-II and also if a continuous infusion of 17-P into the maternal side of the cotyledon would have a similar effect.

STUDY DESIGN: Two cotyledons were obtained from each of five placentas at the time of cesarean section. A chorionic artery and vein pair were cannulated in each cotyledon and perfused with a balanced Hank's and albumin solution. After thirty minutes, one of the cotyledons was randomly chosen and switched to a continuous infusion of a perfusate containing 17-P. Next, vasoconstricting doses of thromboxane followed by angiotensin-II were injected into each cotyledon's artery and serial perfusion pressures were measured for an additional thirty minutes. This experiment was then repeated on a different set of placentas, perfusing the 17-P continuously into the maternal circulation instead of the fetal arteries.

RESULTS: The continuous infusion of 17-P did not change the perfusion pressure relative to the control cotyledon. Bolus injections of thromboxane and angiotensin-II increased the perfusion pressure of both the 17-P and the control cotyledons but the increase in pressure was significantly less ($p < 0.05$) in the 17-P treated cotyledons.

CONCLUSION: Continuous 17-P infusion into either the fetal or maternal arterial circuits of a placental cotyledon attenuates thromboxane and angiotensin-II induced vasoconstriction in human placentas. To our knowledge, this is the first study to demonstrate that continuous perfusion of the maternal placental circulation with 17-P attenuates vasoactive effects of the fetal placental arteries.

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50 THE INFLUENCE OF MATERNAL OBESITY AND DIABETES ON PLACENTAL LIPID TRAFFICKING

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OBJECTIVE: We hypothesized that hyperinsulinemia and hyperlipidemia regulate the lipid content and expression of lipid droplet-associated proteins in human placental villi and cultured primary human trophoblasts (PHT).

STUDY DESIGN: Venous and cord blood samples were collected from women with obesity (BMI >30, n=8), obesity with gestational or type-2 diabetes (O/DM, n=8), or healthy controls (BMI <25, n=8) undergoing term elective cesarean delivery without labor. PHT cells were exposed to insulin (10 nM) and/or fatty acids mix (1200 M). The levels of triglycerides, cholesterol, non-esterified fatty acids (NEFA), and very long chain fatty acids were analyzed in maternal and fetal blood, as well as in villous biopsies and PHT cells. Total neutral lipids were examined using oil red-O and BODIPY immunofluorescence. The expression of lipid droplet-associated proteins was determined using RT-qPCR.

RESULTS: The O/DM group had higher mean triglyceride levels than the control group (238 +102 vs 131±20 mg/dL, p=0.03). Cord blood triglyceride levels from O/DM women were higher than those from obese women or controls (30.1±16, 14±6, 21±12 mg/dL respectively, $p<0.05$). Other lipids were unchanged among the groups. Although the level of NEFA was elevated and the level of triglycerides was reduced in villi from women with O/DM, compared to obese or controls, there was no enhancement of villous lipid droplets or altered expression of lipid droplet-associated proteins. Using PHT cells we found that insulin and fatty acids increased the expression of lipid droplets and cellular triglyceride content (3-fold, $p<0.05$), along with a 12-fold higher adipophilin expression ($p<0.001$) compared to vehicle control, with no change in the expression of the lipid droplet proteins perilipin, S3-12, or TIP47.

CONCLUSION: Hyperinsulinemia and hyperlipidemia in vivo or in vitro modulate lipid content and selectively regulate the expression of adipophilin in trophoblasts, suggesting that feto-maternal signals stimulates fat efflux from the placenta to the fetus. (Supported by ACOG/Ross-Abbott Award).

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