GENERAL

Abstracts 36 – 43

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36 Effects of fetal nicotine exposure on developmental programming of adult blood pressure and vascular reactivity

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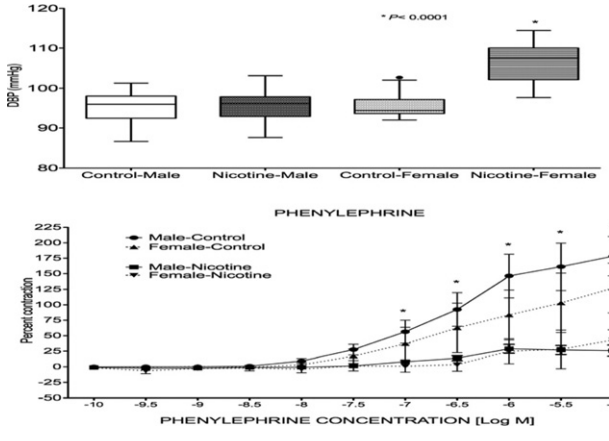
OBJECTIVE: Smoking has been linked to adverse pregnancy outcomes relating to utero-placental insufficiency. We hypothesized that fetuses exposed to nicotine would also have long term consequences relating to developmental programming of cardiovascular function. The aim of this study was to assess long-term cardiovascular effects in offspring exposed to nicotine during development.

STUDY DESIGN: C57Bl/CJ female mice were randomized to drinking water alone or 200mcg/ml nicotine in water starting 2 weeks prior to breeding. Maternal cotinine levels were measured at baseline, prior to breeding and at weaning. When they reached 5 months of age, blood pressure was continuously monitored for 6 days in the unrestrained offsprings by telemetry. They were then sacrificed, and their carotid arteries were isolated for in vitro vascular reactivity studies. One-way ANOVA, Kruksal-Wallis, Student-t and post hoc multiple comparison tests were used for statistical analysis as appropriate (significance: $P<0.05$).

RESULTS: Cotinine levels were minimal in all mice prior to breeding (1.54 +/− 0.05 test group; 0.78 +/− 0.45 mcg/ml control, $P>0.05$). At weaning, maternal cotinine levels were higher in the nicotine group compared to controls (100.0 +/− 9.6 vs 1.49 +/− 0.08 mcg/ml, $P=0.009$). Fetal nicotine exposure increased median systolic and diastolic blood pressure by 8.7-10.6 mmHg and 11.35-13.1 mmHg respectively in female, but not male, offspring ($P<0.001$, Fig. 1). Offspring exposed to nicotine exhibited strikingly blunted vascular contractility in response to phenylephrine (Fig. 2), which was mitigated in the presence of L-NAME, a nitric oxide synthase inhibitor. This effect was more pronounced in male versus female offspring.

CONCLUSION: Nicotine exposure during development produces gender-specific effects on blood pressure and vascular function in adult offspring. This effect appears to be partly endothelial-dependent. We speculate that nicotine alters fetal nicotinic receptor subtype number and activity in the vasculature, in addition to neural pathways contributing to central blood pressure regulation.



37 Diet-induced fetal inflammation is suppressed by maternal metformin

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OBJECTIVE: Obesity and metabolic syndrome is characterized by inflammation and perinatal morbidity and mortality. Metformin (MET), used for treating PCOS and GDM, improves the metabolic profile and may suppress inflammation in the nonpregnant state. Using an animal model of diet-induced obesity/metabolic syndrome during pregnancy, we evaluated the effect of MET on maternal and fetal outcomes.

STUDY DESIGN: Female Wistar rats (6wk old) were fed a normal (NORM) or high fat/high sugar diet (HCAL) for 5wks. After mating with NORM-fed males, half of HCAL-fed dams received MET (300mg/kg PO, daily), and continued their respective diets throughout gestation (N=4-7/group). On GD19 dams were euthanized and outcomes were assessed. Maternal and fetal plasma and placentas were collected and analyzed for MCP-1, TNF, IL-6, leptin and lipids. Data were analyzed using Mann-Whitney and t-test.

RESULTS: HCAL dams gained more prepregnancy weight than NORM (61% vs.47%;$p=0.03$). Pregnancy weight gain was not different (Table 1). HCAL dams had increased plasma triglycerides, chol:HDL ratios, and leptin, and decreased HDL ($P<0.05$). While fetal weights were similar, HCAL-placental weights were slightly decreased (ns). Pups exposed to HCAL diet had elevated plasma IL-6, TNF, and MCP-1 levels ($p<0.05$) and enhanced TNF levels ($p=0.006$) in their placentas (Fig. 1). Maternal plasma cytokines were not different in HCAL dams compared to controls. Maternal MET administration did not impact maternal weight gain, lipid profiles or cytokines, but significantly decreased diet-induced TNF and MCP-1 in the fetal plasma (Fig. 1). No adverse effects of MET on maternal or fetal outcomes were observed.

CONCLUSION: Our model of HCAL diet significantly enhanced fetal inflammation in the absence of maternal inflammation. While MET had no effect on maternal obesity or metabolic markers, it significantly reduced diet-induced fetal inflammation. Given the epidemic of maternal obesity and subsequent impact of in-utero fetal programming, further studies will investigate the potential beneficial effects of MET on the offspring. Supported by Oxenhorn Family.