40 MIDTRIMESTER CERVICAL INFLAMMATORY MILIEU AND SONOGRAPHIC CERVICAL LENGTH

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OBJECTIVE: In vivo, cytokines function as part of an elaborate and complex network. Investigating cytokines individually does not provide insight into their holistic function. In this analysis, we considered cytokines in functional clusters. We explored the relative balance of the pro- and anti-inflammatory cervical milieu as related to midtrimester sonographic cervical length among women with a history of spontaneous preterm birth.

STUDY DESIGN: In a prospective longitudinal cohort of 48 women with a history of spontaneous preterm birth, women were enrolled between 15 and 0/7 and 23 and 6/7 weeks and had 1-6 visits (median 2). At each visit, transvaginal ultrasound for cervical length and pelvic exam for collection of cervical fluid was performed. IL-1β, IL-6 and IL-8 were selected to represent pro-inflammatory cytokines and IL-4, IL-10, and IL-13 were selected to represent anti-inflammatory cytokines. In order to standardize each cytokine, for each woman, the concentration of each cytokine was divided by its median, yielding a multiple of the median (MoM) value. We summed the 3 pro-inflammatory MoMs to generate the pro-inflammatory score, and did the same for the anti-inflammatory score. The relation between cervical length and cytokine milieu was assessed using Generalized Linear Modeling.

RESULTS: The relative balance of pro-inflammatory to anti-inflammatory score had a significant negative linear association with cervical length (β=-0.04, p=0.03) after adjusting for race, smoking, gonorrhea, chlamydia, and bacterial vaginosis.

CONCLUSION: Among women with a prior preterm birth, shorter cervical length is associated with a relatively more pro-inflammatory cervical milieu. This novel finding suggests that cervical shortening is not simply anatomic but is also associated with biochemical and immunological changes, suggesting opportunities for future mechanistic and interventional research.

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41 SYNERGISTIC EFFECT OF PREPREGNANCY OBESITY AND SFLT1-INDUCED PREECLAMPSIA ON FETAL PROGRAMMING OF ADULT VASCULAR FUNCTION

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OBJECTIVE: To test the hypothesis that prepregnancy obesity and sFlt1-induced preeclampsia lead to altered vascular function in the offspring later in life.

STUDY DESIGN: CD-1 female mice were placed on low (LF; 4.3 gm% fat) or high fat (HF; 34.9 gm% fat) diet for 12-14 weeks before mating. On day 8 of pregnancy, mice in the HF group were injected with adenovirus carrying sFlt1 (HFsFlt1 group) or adenovirus carrying mFc as virus control (HFmFc group). After weaning, all offspring were placed on a standard diet containing 5.6% fat. At 12 weeks of age, the right carotid artery was isolated for in-vitro vascular reactivity studies (n=10-12 per group). Concentration-response curves to phenylephrine, thromboxane, serotonin, acetylcholine, sodium nitroprusside and isoproterenol were obtained. ANOVA with Bonferroni post hoc test were used for analysis (significance: p<0.05).

RESULTS: At the time of breeding, HF mice were significantly heavier than LF. There were no differences in pup weight, weight at 12 weeks, weight of visceral fat, or visceral fat/body weight ratio between the groups when comparing within the same gender. Males in all groups were significantly heavier than females, with no difference in fat tissue weight. In HFsFlt1 group, fasting glucose was significantly higher in males compared with females. Responses to serotonin in males and to thromboxane in females were significantly lower in both HF groups compared to the LF group. Among males, responses to phenylephrine were significantly lower in HFsFlt1 compared to HFmFc or LF. Within the HFsFlt1 and LF groups, responses to phenylephrine were significantly lower in females compared to males. Responses to thromboxane were lower in females versus males in both HF groups, but not in the LF group.

CONCLUSION: Prepregnancy obesity alters fetal programming of adult vascular function, and this effect is amplified by preeclampsia, particularly in female offspring. The mechanism is complex and gender-specific. Prevention of prepregnancy obesity or preeclampsia can have significant impact on long term health in the offspring.

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42 THE ROLE OF TRANSFORMING GROWTH FACTOR ETA IN CERVICAL REMODELING

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OBJECTIVE: Transforming growth factor 1 (TGF1) is a multifunctional cytokine which acts to regulate proteins of the extracellular matrix. It has been shown to increase the production of collagen and proteoglycans. Because both substances are thought to play a role in cervical remodeling, we hypothesized that TGF1 and its receptors would increase in early gestation before decreasing at term. This study therefore aims to determine the expression of TGF1 and its receptors in the cervix during pregnancy.

STUDY DESIGN: The cervix of non pregnant and timed pregnant rats at days 12, 16, 18, 20, 21 and 22 of gestation were obtained and analyzed for mRNA expression of TGF1, TGF-Receptor 1 (TR1), TR2, and TR3 using a 5′endonuclease assay. Multiplex assays were performed in triplicate using -actin as an internal control. Four animals were sacrificed for each time point using an IACUC approved protocol. Western blotting was used to determine protein concentration. Blots were normalized using -actin. SMAD phosphorylation was assessed to confirm activation of TGF1 signaling pathway. Data was analyzed using ANOVA.

RESULTS: TGF1 mRNA increased through day 21 before declining on day 22 of gestation (ANOVA p=0.001). The mRNA expression of TR1 and TR2 did not change with advancing gestation. TR3 m-RNA expression followed a similar pattern as TGF1 and increased through day 18 before a sharp decline was seen on day 22 of gestation (ANOVA p=0.001). Western blot analysis of TR3 protein expression followed a similar pattern to the mRNA expression (ANOVA p=0.017). Increased SMAD phosphorylation paralleled changes in TR3.

CONCLUSION: TR3 is known to increase TR1 activation by facilitating TR2-ligand interactions. Collagen type 1, the main stress bearing structural protein, also increases through pregnancy. It is possible that changes within the cervical extracellular matrix are regulated by signaling between TGF1 and TR3.

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43 FETAL PROGRAMMING OF HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA IS EVIDENT IN YOUNG ADULTHOOD

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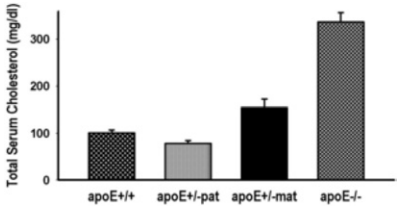
OBJECTIVE: We have previously described a model of developmental programming of atherosclerosis in which heterozygous mice born to apoE-knockout mothers were affected by high cholesterol levels, atherosclerotic plaques, and renal and hepatic lesions at 8 months of age. Our objective in this study was to determine whether this process can be detected earlier in life.

STUDY DESIGN: We crossbred apoE knockout (apoE−/−) and wild-type C57BL/6J (apoE+/+) mice to obtain heterozygous offspring born to hypercholesterolemic apoE−/− mothers (apoE+/−mat, n=17), heterozygous offspring born to wild-type mothers (apoE+/−pat, n=16), homozygous knockout offspring (apoE−/−, n=18), and homozygous wild-type offspring (apoE+/+, n=17). The resulting pups were followed until 4 months of age when they were sacrificed. Serum samples were obtained, and levels of total cholesterol and total triglycerides were measured using colorimetric enzyme assays.

RESULTS: At 4 months of age, we found significant differences in total cholesterol and triglyceride levels across the study groups (p<0.001 and p<0.007, respectively). Total cholesterol levels in apoE+/−mat offspring were higher than in apoE+/−pat (p<0.001) and apoE+/+ (p=0.006), and lower than in apoE−/− (p<0.001) offspring. Triglyceride levels were similar in apoE+/−mat and apoE−/− animals. ApoE+/−mat displayed higher triglyceride concentrations than apoE+/+ mice (p=0.006), while the difference with apoE+/−pat offspring did not reach statistical significance (p=0.137).



CONCLUSION: The present data validate our previous finding of a significant effect of the maternal environment on cholesterol levels in the apoE mouse model. In addition, we have found that the effect on cholesterol and triglyceride levels is demonstrable in the offspring during young adulthood, providing an early opportunity for prevention of adult diseases.

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