263 IN VITRO UTERINE ARTERY REACTIVITY IN A PREGNANT MOUSE MODEL OF PREECLAMPSIA INDUCED BY OVER-EXPRESSION OF SFLT-1. FANGXIAN LU[1], NIMA GOHARKHAY[1], EGLE BYTAUTIENE[1], ESTHER TAMAYO[1], GARY DV HANKINS[1], MONICA LONGO[1], GEORGE R SAADE[1], [1]The University of Texas Medical Branch, Obstetrics and Gynecology, Galveston, Texas

OBJECTIVE: We have previously validated a mouse model of preeclampsia induced by adenovirus-mediated over-expression of sFlt-1. Our objective was to further investigate the underlying mechanisms for the preeclampsia-like condition in this animal model by evaluating the vascular reactivity of the uterine artery.

STUDY DESIGN: At day 8 of gestation, CD-1 mice were randomly allocated to injection of the adenovirus carrying Flt (1-3) [AdFlt(1-3); 10^9 PFU] or adenovirus carrying mFc control (10^9 PFU) via the tail vein (n=6/group). At day 18 of gestation, the mice were sacrificed and 2 mm segments of uterine artery were mounted in a wire myograph for isometric tension recording. Contractile responses to phenylephrine (PE, 10^{-10} - 10^{-5} M) were assessed in the presence and absence of L-NAME, an inhibitor of nitric oxide synthase. In addition, concentration-response curves to the endothelium-dependent relaxing agent acetylcholine (Ach, 10^{-10} - 10^{-5} M), the endothelium-independent relaxing agent sodium nitroprusside (SNP, 10^{-10} - 10^{-5} M), and thromboxane A_2 (TxA_2, 10^{-10} - 10^{-6} M) were obtained. Student *t* test was used for statistical analysis (significance: $p<0.05$).

RESULTS: The maximal response to PE in the sFlt-1 group was significantly higher compared with control (187.98 ± 15.13 vs 118.70 ± 9.29 %, P=0.008), but this difference was abolished in the presence of L-NAME. The relaxation to Ach was significantly decreased in the sFlt-1 group compared with control (28.27±12.3 vs 86.79±4.86 %, P=0.007). No differences were noted in the SNP and TXA_2 responses.

CONCLUSION: The previously characterized preeclampsia-like condition induced by over-expression of sFlt-1 is accompanied by impaired uterine vascular reactivity, likely due to endothelial dysfunction. We speculate that this altered vascular function leads to impaired placenta perfusion and preeclampsia. Further investigations focusing on the uterine vasculature and the underlying pathologic mechanisms in this animal model are warranted.

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264 IN SEVERE PREECLAMPSIA, ACTIVATION OF THE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS (RAGE) SYSTEM OCCURS INDEPENDENT OF ANTIGENIC N-CARBOXYMETHYL-LYSINE MODIFIED PROTEINS MARGARET A. BAUMBUSCH[1], CATALIN S. BUHIMSCHI[1] GUOMAO ZHAO[1], EMILY A. OLIVER[2], IRINA A. BUHIMSCHI[1], [1]Yale University, Ob/Gyn & Reprod Sci, New Haven, Connecticut, [2]King's College London, Women's Health, London, United Kingdom, United Kingdom

OBJECTIVE: Severe preeclampsia (sPE) is characterized by RAGE system activation, which leads to inflammation, oxidative stress and endothelial injury. The putative stimulus remains unknown. One candidate is the antigenic N-carboxymethyl-lysine (CML), an advanced glycation end-product (AGE) formed by the nonenzymatic glycation of proteins. This study was conducted to determine if CML and CML auto-antibodies may be responsible for activation of the RAGE system in women with sPE.

STUDY DESIGN: In a case control study we analyzed time-matched samples of blood and urine from 118 women with either sPE (n=79, GA: 31 [22-36] wks) or uncomplicated pregnancies delivered at term (CRL n=39, GA: 30 [21-34] wks). Circulating soluble RAGE (sRAGE) served as a marker of RAGE activation. Levels of CML, CML auto-antibodies and sRAGE were assessed by sensitive and specific immunoassays. Urine analytes were normalized to creatinine. In addition, we employed immunolocalization for CML in placental tissue sections from women with sPE (n=6). We used as control placental tissues from GA matched women with idiopathic preterm birth and no histological chorioamnionitis (n= 6).

RESULTS: **1**) In women with sPE, increased circulating levels of sRAGE proved RAGE system activation (sPE vs. CRL, $P<0.001$); **2**) CML and CML auto-antibodies were detectable in blood and urine of healthy CRLs, but no differences were seen in comparison to sPE; **3**) There was no correlation between circulating and urinary CML or CML auto-antibodies with sRAGE; **4**) Though clumpy deposits of CML immunoreactive proteins in decidua, villous stroma, and maternal vascular spaces were seen, there were no discernable differences among the groups.

CONCLUSION: We provide evidence that RAGE system activation in sPE may occur through a pathway independent of AGEs.

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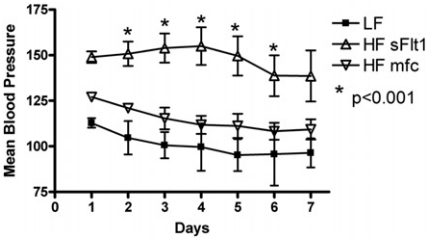
265 FETAL PROGRAMMING OF ADULT BLOOD PRESSURE IN A MOUSE MODEL OF PRE-PREGNANCY OBESITY AND PREECLAMPSIA. EGLE BYTAUTIENE[1], ESTHER TAMAYO[1], FANGXIAN LU[1], PHYLLIS GAMBLE[1], GARY DV HANKINS[1], MONICA LONGO[1] GEORGE R SAADE[1], [1]The University of Texas Medical Branch, Obstetrics and Gynecology, Galveston, Texas

OBJECTIVE: To test the hypothesis that pre-existing maternal obesity and preeclampsia lead to altered blood pressure in the offspring later in life, using well-established mouce models of obesity and preeclampsia-like syndrome induced by sFlt-1 overexpression.

STUDY DESIGN: CD-1 female mice were place on either low fat (LF; 4.3 gm% fat) or high fat (HF; 34.9 gm% fat) diet for 12-14 weeks before mating. On day eight of pregnancy, mice in the HF group were injected with adenovirus carrying sFlt1 (HFsFlt1) or adenovirus carrying mFc as virus control (HFmFc). After weaning, offspring from the 3 groups were placed on a standard diet containing 5.6% fat (n=10-12 per group). At 12 weeks of age, blood pressure (BP) was measured continuously in conscious unrestrained male offspring using implanted telemetric transducers. One-way and repeated measure ANOVA with Bonferroni post hoc test were used for analysis (significance $p<0.05$).

RESULTS: There were no differences in weight at birth, body weight at 12 weeks of age, weight of visceral fat, or visceral fat/body weight ratio between the offspring groups. Locomotor activity was significantly lower in offspring from HFsFlt1 group compared with LF ($p<0.04$). Mean and systolic BP were significantly higher in offspring born to HFsFlt1 group mothers compared with the other groups ($p<0.001$). There were no differences in diastolic BP, heart rate, or pulse pressure between the 3 groups.



CONCLUSION: Pre-pregnancy maternal obesity with superimposed sFlt1-induced preeclampsia, but not obesity alone, leads to hypertension and lower motor activity in the offspring later in life. Prevention of pre-pregnancy obesity and/or preeclampsia can have significant impact on long term health in the offspring.

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