Title

312: Maternal extracellular miRNAs as biomarkers for placental dysfunction between 17-28 weeks gestation

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and preeclampsia, we hypothesized that the administration of pravastatin could attenuate the expected cardiac changes with hypertensive disorders as demonstrated by the SRUPP model.

STUDY DESIGN: Pregnant Sprague-Dawley rats were allocated to one of four groups: sham surgery (n=12), SRUPP surgery (n=12), sham surgery with pravastatin (n=9), and SRUPP surgery with pravastatin (n=10). On gestational day (GD) 13, all pregnant rats underwent maternal echocardiography. On GD 14, the SRUPP surgery and SRUPP surgery with pravastatin groups underwent laparotomy with placement of silver clips on the uterine and utero-ovarian arteries bilaterally. In the sham surgery groups, the uterine and utero-ovarian vessels were isolated without placement of clips. The rats in the pravastatin groups were administered 1 mg/kg pravastatin on GD 14 through 19. On GD 20, all pregnant rats underwent repeat maternal echocardiography. Analysis of Variance (ANOVA) was used for statistical analysis. Post hoc multiple comparison tests were performed as well. A P value <0.05 indicated statistical significance.

RESULTS: The echocardiogram parameters did not differ significantly among groups on GD 13. On GD 20, the cardiac output in the rats in the SRUPP surgery group (64.67 ± 2.03 mL/min) was significantly increased compared to the sham surgery group (49.35 ± 3.58 mL/min) (P = 0.008). Additionally, the stroke volume differed significantly between the SRUPP surgery group (166.29 ± 6.19 uL) and the sham surgery group (135.20 ± 9.35 uL) (P = 0.047). While not statistically significant, the cardiac output (56.97 ± 4.23 mL/min) was decreased in the SRUPP surgery with pravastatin group as compared to the SRUPP surgery group (P=0.09).

CONCLUSION: Pravastatin may attenuate the expected changes in cardiac function with hypertensive disorders as seen in the SRUPP model of preeclampsia in rats.

312 Maternal extracellular miRNAs as biomarkers for placental dysfunction between 17-28 weeks gestation

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OBJECTIVE: We used next-generation sequencing methods to identify miRNAs in the extracellular RNA in the serum of patients between 17-28 weeks gestation in patients who developed placental dysfunction (preeclampsia or intrauterine growth restriction) compared to those with uncomplicated pregnancy outcomes.

STUDY DESIGN: Maternal serum was collected between 17-28 weeks gestation from the UC San Diego Placental Dysfunction Clinic. Subjects were referred to the clinic for abnormal analytes from first or second trimester serum aneuploidy screening or maternal co-morbidites that increased their risk for placental dysfunction. 19 cases and 29 controls were selected from this cohort. Extracellular RNA was isolated from the serum samples, and small RNA sequencing libraries were constructed. Differential rank conservation was used to identify extracellular miRNA biomarkers associated with placental dysfunction.

RESULTS: The UCSD cohort was analyzed in two technical replicates. To avoid normalization artifacts, ratios of pairs of miRNAs were used as analytes. The performance of all possible pairs of detected miRNAs was determined separately for the two technical replicate datasets for this cohort. The 100 top performing miRNA pairs from the first technical replicate of the UCSD cohort were selected for further analysis. There was an enrichment of miRNAs encoded by two miRNA gene clusters on chromosomes 14 and 19, both of which have been reported to be expressed in the placenta in prior studies. The performance of all possible combinations of 5 pairs from these 100 top performing miRNA pairs were tested. The best combinations of 5 miRNA pairs yielded a sensitivity of 94.4% and specificity of 96% in the first technical replicate and a sensitivity of 93% and specificity of 89.5% in the second technical replicate. The performance of these combinations in a sample set including only normal versus severe preeclampsia cases only, and obtained a sensitivity and specificity of 100% for the top performing combinations in both the first and second technical replicates.

CONCLUSION: By isolating and performing small RNA sequencing on extracellular RNA from maternal serum collected between 17-28 weeks gestation, we identified candidate biomarkers for placental dysfunction miRNAs in the maternal serum. Future work will include validation of these candidates in an independent cohort.

313 Quantitative functional alterations in complement alternative pathway and related genetic analysis in severe phenotype preeclampsia and HELLP syndrome

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OBJECTIVE: Preeclampsia and HELLP syndrome share many clinical and biologic features with thrombotic microangiopathy syndromes caused by abnormalities in complement pathways. It is unclear whether functional and genetic alterations in the complement alternative pathway (CAP) are associated with preeclampsia and HELLP syndrome.

STUDY DESIGN: We used prospectively collected blood samples (2012 to 2016) from cases of severe phenotype preeclampsia, defined as delivery <34 weeks, HELLP syndrome and eclampsia, and matched normotensive controls (n=25 in each arm). Quantitative and functional analysis of 15 CAP components and activation fragments was conducted using clinically available immunoassays. Whole exome sequencing was performed on study group to interrogate 36 genes encoding CAP factors for coding non-synonymous sequence variants with a population allele frequency of <5%.

RESULTS: Study and control groups were similar in age, gravidity, parity, marital status and race. However, the study group had a higher BMI (mean±SD; 32±8 vs 25±4 kg/m^2; p=0.002) and earlier gestational age at delivery (32.5±3.6 vs 40.3±1 weeks; p<0.001). Serological studies in cases compared with controls demonstrated elevated Bb subunit (median [range]; 1.2 [0.5-4.3] vs 0.6 [0.5-1] mcg/mL; p<0.001), C5 concentrations (28 [18-33] vs 24 [15-34] mg/dL; p=0.03) and sMAC (371 [167-761] vs 184 [112-249] ng/mL; p<0.001) levels. Of 25 cases, 17 (68%) had at least 1 sequence variant in CAP genes (5 x *CFB*, 2 x *CFI*, 3 x *CFH*, 5 x *CFHR*, 1 x *MCP*, 5 x *C2*, 3 x *C3*, 1 x *C3R*, 1x *C5*, 5 x *C7*, 5 x *C8*, 1x *C9*). Specific listings are found in **Figure**.

CONCLUSION: Patients with severe phenotype preeclampsia manifest functional alterations in complement alternative pathway activation, as evident by elevated levels of Bb, C5 and sMAC. Associated genetic sequence variants in complement pathway genes are also more common than expected, some of which are potentially pathogenic, suggesting shared genetic pathogenesis. Genetic screening and