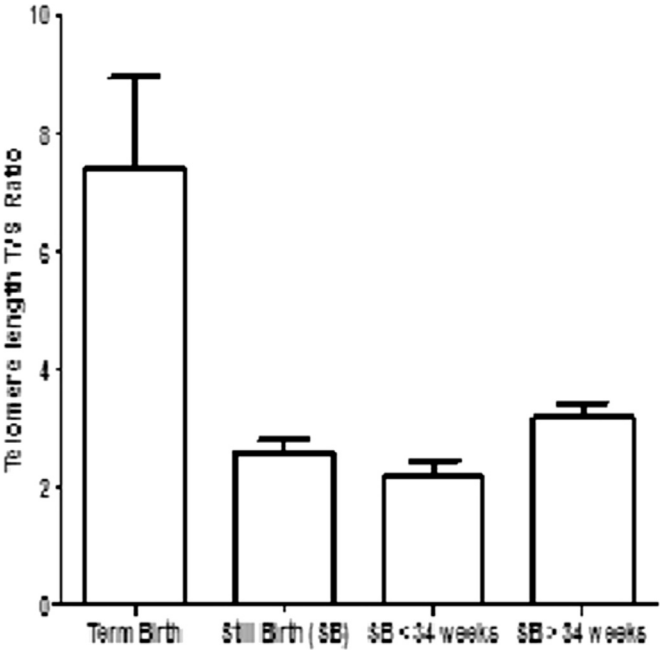
study was to evaluate placental telomere shortening as an indicator of premature senescence and oxidative stress in SB.

STUDY DESIGN: Placental tissue was collected from 27 antepartum unexplained SB (> 22 weeks) from a consecutive series of 51. Thirty-seven healthy controls (term) were randomly collected, matched for maternal age and ethnicity. SB was categorized as unexplained after an extensive workup to exclude known causes such as congenital/genetic anomalies, infection, twin to twin transfusion syndrome and hypoxia. DNA was extracted from the placenta for telomere length analysis using real time PCR. Standard curves were generated for telomere lengths from single copy gene amplifications using reference DNA. The telomere length for each sample was based on the ratio of telomere length of the sample to the single copy gene standard (T/S ratio) using the formula: ΔCt [Ct(telomere sample)/ Ct(single gene)]. Telomere length was expressed as a relative T/S ratio normalized to the average T/S ratio of the reference sample [2-(ΔCtx -ΔCtr) = 2-$\Delta\Delta$Ct]. ANOVA was used for statistical analysis.

RESULTS: Placental telomere length was 3 fold lower in SBs compared with control (T/S mean + SD: 2.604±1.204 vs. 7.406 ±8.035; $p < 0.001$). When data were stratified by early (< 34 weeks; mean gest age 27.8 weeks) and late SBs (above 34 weeks; mean gest age 38.25 weeks), telomere lengths remained significantly lower (early SB T/S: 2.193±1.21; late SBs T/S: 3.208±0.93; both $p < 0.01$ compared to control).

CONCLUSION: Reduction in telomere length in SBs is indicative of placental senescence likely due to oxidative stress in response to specific risk exposure. These data support a role for premature placental ageing in the etiology of unexplained SBs and provide a novel mechanistic insight.



8 Epigenetics and microRNA as a unifying mechanism in severe preeclampsia

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OBJECTIVE: Environmental factors can cause epigenetic & microRNA(miRNA) changes that may be associated with increased susceptibility to preeclampsia(PE). DNA methylation, histone modification, and miRNA regulation orchestrate a complex epigenetic signature without altering the gene sequence, while regulating gene expression. Our objective was to investigate the relationship between first trimester epigenetic & miRNA interaction in severe PE(SPE).

STUDY DESIGN: Case control study of patients presenting for aneuploidy screening at 11-14 weeks gestation. In an initial study, DNA methylation was measured via Comprehensive High-throughput Arrays(CHARM) on 6 cases(SPE) & 6 controls. Infinium HumanMethylation450 was run on 12 additional SPE and 24 controls. Genome studio was used to calculate average β values which were corrected for multiplicity. TaqMan Array was used to determine miRNA & epigenetic enzyme gene expression. Only expression with a Cq $\leq$ 32 were included (DataAssis -corrected for false discovery rate). U6(Normfinder) was used as the reference. Post-translationally modified histones were measured by reverse-phase liquid chromatography mass spectrometry. Target scan, mirBASE & Ingenuity Pathway were used to develop an underlying mechanism for the development of SPE.

RESULTS: 81 hypomethylated genes were associated with SPE(30-45% changes noted in the SPE vs controls in CHARM). 86 CpG islands with q-values of 0.01 were identified using the Infinium. Of the 86 sites, 54 were associated with genes(4 hyper- & 50 hypomethylated). 35 miRNAs were up regulated in SPE($p<0.05$). Increased H4 acetylation was observed in SPE patients. Six epigenetic genes including HDAC5 showed significant changes in SPE($P<0.05$). Figure shows a putative model of above findings.

CONCLUSION: Using a comprehensive approach incorporating assessment of epigenetics and miRNA, we discovered a novel interactive model which may account for the development of SPE. This discovery may prove to be useful in identifying first trimester markers for the prediction of SPE.