17 EPIGENETIC MODULATION OF ENDOGLIN AND VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 1 (FLT-1) IN SEVERE PREECLAMPSIA

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OBJECTIVE: Epigenetics is the study of pretranscriptional modifications of genomic DNA. Specifically, methylation of CpG base pairs within the gene's promoter region effectively silences gene activity. Endoglin and Vascular Endothelial Growth Factor Receptor −1 (Flt-1) have been shown to be associated with preeclampsia. Previous analysis of these genes in cancer have demonstrated significant epigenetic modulation. In this study, we investigated whether differential gene methylation occurs in preeclampsia compared to unaffected pregnancies.

STUDY DESIGN: Five placentas each from severe preeclamptic placentas and mild preeclamptic placentas were investigated. Seven normal placentas served as controls. The diagnosis of preeeclampsia was based upon strict ACOG criteria. Genomic DNA was extracted from fresh placental tissue then analyzed by COmbined Bisulfite Restriction Analysis or COBRA. If differential digestion was seen between normal and preeclamptic placentas, further analysis was performed by cloning and DNA sequencing.

RESULTS: Flt-1 demonstrated more digestion within the normal and mild preeclamptic placentas than in the severe preeclamptic placentas. Sequencing revealed a significant increase in the methylation of CpG bases in normal and mildly preeclamptic placentas. Severely preeclamptic placentas demonstrated minimal methylation of CpG bases. The gene for Flt-1 was significantly de-methylated in placentas from women with preeclampsia compared to controls, indicating a mechanism for transcriptional induction. On the other hand, no differences in the methylation of Endoglin was found in preeclampsia.

CONCLUSION: We speculate that demethylation of Flt-1, leading to the induction of Flt-1 and its truncated portion sFlt-1, appears to underlie the pathophysiology of preeclampsia.

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