DIABETES MELLITUS AND PREECLAMPSIA: PRAVASTATIN PROTECTS AGAINST GLUCOSE-INDUCED CYTOTROPHOBLASTS DYSFUNCTION: A TRANSLATIONAL APPROACH

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Abstract: Despite growing knowledge of the pathophysiology involved in the development of preeclampsia (PreE) and diabetes mellitus (DM), the interactions between the two disease processes need to be further examined. An increasing level of evidence supports the utility of pravastatin in prevention against preE. We previously demonstrated that hyperglycemia induces cytotrophoblasts (CTBs) dysfunction characteristic of a preE-like phenotype. This study compared normal pregnancies to those complicated with preE, gestational diabetes, and/or pre-existing DM in order to assess the effect of elevated glucose on placental development and its potential role in the pathogenesis of preE. We also sought to demonstrate the utility of pravastatin in rescuing CTBs from hyperglycemia induced dysfunction. The chart review was performed in an IRB approved retrospective cross-sectional study resulted in live born singleton deliveries. Total 621 subjects were randomly selected from deliveries in 2008 through 2011 at Scott & White Memorial hospital. Human CTBs were treated with 100, 150, 200, 300, or 400 mg/dL glucose for 48h. Some cells were pretreated with pravastatin (1ug/mL) for 2h, while others were co-treated with pravastatin (1ug/mL) prior to glucose treatment. Some cells were treated with D-Mannitol. Cell migration was performed by Matrigel migration assay kit according to manufacturer protocol. Cell lysates were utilized to evaluate the expression of urokinase plasminogen activator (uPA), plasminogen activator inhibitor 1 (PAI-1), proliferating cell nuclear antigen (PCNA) and p38 MAPK phosphorylation by western blot. Levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), soluble fms-like tyrosine kinase-1 (sFlt-1), soluble endoglin (sEng) and interleukin 6 (IL-6) were measured in culture media using ELISA kits. Statistical comparisons were performed using analysis of variance with Duncan’s post hoc test. Patients who developed preE during gestation had higher blood pressures for both Systolic and Diastolic compared to the group who did not developed preE during pregnancies (p < 0.05). Patients with either DM prior to pregnancy or developing gestational diabetes were older. Patients with preE delivered earlier in pregnancy than those without preE regardless of diabetes status. However, those with preE and pre-existing DM delivered significantly earlier at 35.0 +/- 0.4 than the other two preE groups (*p < 0.05 for each), suggesting more severe condition. Additionally, patients with pre-existing DM who developed preE delivered smaller babies than those with pre-existing DM without preE (1.00 ± 0.03, p < 0.05 for each). However, the development of gestational diabetes did not result in smaller babies for those pregnancies with preE. Hyperglycemia inhibited CTBs migration, down-regulated uPA, PAI-1, PCNA and up-regulated p38 phosphorylation in CTBs treated ≥150 mg/dl of glucose (*p < 0.05 for each). Secretion of sFlt-1, sEng and IL-6 were increased while VEGF and PIGF were decreased in CTBs treated >150 mg/dL glucose compared to basal (100 mg/dL) (*p < 0.05 for each). Secretion of sFlt-1, sEng and IL-6 were increased while VEGF and PIGF were decreased in CTBs treated >150 mg/dL glucose (*p < 0.05 for each). Both pravastatin pretreatment and co-treatment significantly rescued CTBs migration, up-regulated uPA, PAI-1, PCNA, down-regulated p38 phosphorylation, and corrected the angiogenic profile of CTBs (p < 0.05 for each). D-Mannitol had no effect on CTBs. The development of preE in those with pre-existing DM led to growth restriction and more severe disease as evidenced by lower birth weights and earlier gestational ages at delivery. This supports the concept that elevated glucose levels during placental development in the first trimester may alter the placenta and lead to restriction later in pregnancy when a second stimulus triggers preE. Pravastatin mitigates the hyperglycemia-induced dysfunction of CTBs These data should alleviate critical concerns regarding pravastatin use on CTBs development early in pregnancy and support the current research to use of pravastatin in preE prevention.