Enhanced Placental Angiopoietin-like Protein 2 Levels in Fetal Growth Restriction

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OBJECTIVE: Angiopoietin-like protein 2 (ANGPTL2) maintains cell stemness by preventing differentiation and promotes endothelial dysfunction by impairing endothelium-dependent vasorelaxation. Angptl2 also acts as pro-inflammatory mediator in metabolic syndromes, atherosclerosis, and tissue injury. Mesenchymal to hemangiogenic cell differentiation is crucial for adequate placental vasculogenesis. Inadequate vascularization and/or endothelial dysfunction causes placental insufficiency, a primary feature of fetal growth restriction (FGR). Thus, we hypothesize that FGR-associated placentas display elevated levels of ANGPTL2, that contribute to inadequate vascularization and/or endothelial dysfunction.

STUDY DESIGN: After obtaining written consents, placental villi were obtained from gestational age and maternal BMI-matched control and FGR-complicated pregnancies (n=10/each) and analyzed by qPCR and immunohistochemistry. ANGPTL2 mRNA levels after β-actin normalization were calculated using the 2^ΔΔCt values. Paraffin sections were immunostained with ANGPTL2 antibody and evaluated by a histologic scoring (HSCORE). Results were analyzed using a t-test with P < 0.05 considered statistically significant.

RESULTS: Significantly higher ANGPTL2 mRNA levels were found in FGR complicated vs. control placentas (Mean/SEM: 2.90/0.48 vs. 1.24/0.27, P=0.008). In placental villi, ANGPTL2 immunoreactivity were primarily detected in endothelial, mesenchymal and Hofbauer cells of the mature and immature intermediate villi, with no staining in villous cytotrophoblasts and syncytiotrophoblasts. ANGPTL2 HSCORE was significantly higher in FGR-complicated vs. control placentas (143.62/18.61 vs. 49.48/6.72, P < 0.001).

CONCLUSION: These results show that FGR is associated with elevated placental ANGPTL2 mRNA and protein levels. We postulate that such elevations impair placental vasculogenesis and/or endothelial dysfunction to cause placental insufficiency. Further studies are required to determine whether enhanced ANGPTL2 levels is a cause or effect of FGR and whether it can serve as a biomarker of impending FGR.