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Reproductive Endocrinology

IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH

ANGPTL3 Levels in Healthy and Mild Preeclamptic Pregnant Women

Maria F. Garces, BS, MSC, PhD¹, Roberto Franco - Vega, MD¹, Luis M. Maldonado - Acosta, MD², Andres Castro - Pinzón, MD¹, javier Eslava-Schmalbach, MD, PhD¹, Arturo J. Parada - Banos, MD¹, Edith Angel-Müller, MD¹, Rubén Nogueiras, PhD³, Carlos Dieguez, MD, PhD³, Justo castaño, MD, PhD⁴, Ariel I. Ruiz-Parra, MD¹, Jorge Eduardo Caminos, PhD¹.

¹Universidad Nacional de Colombia, Bogota, Colombia,

²Universidad Nacional de Colombia, Santafé De Bogota,

Colombia, ³Universidad de Santiago de Compostela, Santiago De

Compostela, Spain, ⁴Universidad de Córdoba, Córdoba, Spain.

Introduction: Throughout normal pregnancy, different metabolic and hormonal adaptations are presented, among others, significant modifications in the profile of lipids and lipoprotein metabolism. On the other hands, Angiopoietin-like protein 3 (ANGPTL3) are involved in the regulation of triglyceride metabolism in the fed state by inhibiting the enzyme lipoprotein lipase in oxidative tissues. **Objective:** Thus, the objective of this study was to determine the profile of serum ANGPTL3 levels during three periods of gestation and three months after delivery. **Design, setting and Participants:** Serum ANGPTL3 levels were analyzed by ELISA, throughout pregnancy in a case-control study nested within a longitudinal prospective cohort of healthy pregnant (n = 52) and mild preeclamptic women (n = 20), women in the third month postpartum (n = 20) and healthy non-pregnant women (n = 20). The results obtained were correlated with biochemical, hormonal, and anthropometric variables. **Results:** A significant reduction in ANGPTL3 levels was observed from the first to the third trimesters of pregnancy in healthy and preeclamptic pregnant women when compared with healthy non-pregnant and postpartum women (p<0.01). There were no significant differences in serum ANGPTL3 levels between normal and preeclamptic women. Serum ANGPTL3 levels were positively correlated with triglyceride, very-low-density lipoprotein cholesterol, and total cholesterol levels in healthy non-pregnant (p<0.05); whereas there were no significant correlations between ANGPTL3 with the same variables in healthy and preeclamptic pregnant women. Besides, there were no significant correlations between serum ANGPTL3 with body mass index, high-density lipoprotein cholesterol, glucose, insulin, leptin or HOMA-IR in the study groups described above. **Conclusions:** The results of the present study show for the first time that ANGPTL3 could be playing a fundamental role in the homeostasis of lipid metabolism throughout gestation. Thus, low levels of ANGPTL3 during pregnancy might favor the accumulation of lipid in oxidative tissues as

a deposit of maternal energy source, while preserving glucose and amino acids for the fetus.

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BMP6 Mediates BMP2-Increased Human Trophoblast Invasion

Jianye Deng, Doctor¹, Yan Li, MD, PhD².

¹Shandong University, jinan, China, ²SHANDONG UNIVERSITY, Jinan, China.

TGF- β superfamily proteins play divergent roles in regulating human extravillous trophoblast (EVT) invasion and their coordinated effects are essential for adequate placentation during pregnancy ¹. Bone morphogenetic protein 2 (BMP2), which belongs to the BMP subfamily of TGF- β superfamily, has been shown to promote human EVT invasion and the acquisition of endothelial-like phenotype ^{2,3}. It has been reported that BMP2 promotes EVT invasion by up-regulating Activin A, a growth factor which also belongs to TGF- β superfamily. However, whether BMP6 mediates the pro-invasive effect of BMP2 has yet to be determined. Herein, we firstly treated immortalized trophoblast cells (HTR8/SVneo) with recombinant BMP2 protein for 6 and 24 hrs, and our bulk-RNA sequencing results demonstrated significantly increased BMP6 mRNA levels after BMP2 treatment. Furthermore, we confirmed the up-regulatory effects of BMP2 on BMP6 mRNA and protein levels in both HTR8/SVneo and primary EVTs isolated from first-trimester villi. Notably, siRNA-mediated down-regulation of BMP6 significantly attenuated both basal and BMP2-induced cell invasion in HTR8/SVneo cells as measured by Matrigel-coated transwell invasion assay. In summary, our results firstly demonstrated the up-regulatory effect of BMP2 on BMP6 expression in human trophoblasts and identified the mediation role of BMP6 in BMP2-promoted EVT invasion, suggesting the interplay between BMP subfamily members during EVT invasion regulation. Our ongoing research focusing the underlying molecular mechanisms and signaling pathways could further benefit the advancement of diagnostic and therapeutic strategies for EVT invasion dysregulation-related pregnancy disorders, e.g., pre-eclampsia. **Reference:** (1) Li Yan et al., *Trends Endocrinol Metab* 2021 18: S1043-2760(20)30266-6. (2) Hong-Jin Zhao et al., *FASEB J* 2020;34(2):3151-3164. (3) Hong-Jin Zhao et al., *Cell Death Dis* 2018;9(2):174.

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Bone Morphogenetic Protein 2 Increases Human Trophoblast Invasion by Up-Regulating Integrin Beta3

Cuiping Hu, MS, Junhao Yan, MD.

Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University, National Research Center for Assisted Reproductive Technology and Reproductive Genetics, The Key