and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22(1):141-146.4. Rubin KH, Glintborg D, Nybo M, Abrahamsen B, Andersen M. Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2017;102(10):3848-3857.

Reproductive Endocrinology
IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH
ANGPTL3 Levels in Healthy and Mild Preeclamptic Pregnant Women
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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
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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. 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. 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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The adequate invasion of extravillous trophoblast cells (EVTs) is indispensable for the implantation of embryos and subsequent remodeling of uterine spiral arteries in early human gestation. Bone morphogenetic protein 2 (BMP2), which is abundantly expressed at the maternal-fetal interface, has been shown to promote the human EVT invasion process (1). Integrin switching (i.e., a switch from α6β4 to αvβ3) plays essential roles in cell-extracellular matrix adhesion and has been reported to influence EVT migration and invasion (2). Moreover, integrin β3 has been found to promote the adhesion, invasion, and migration abilities of embryonic trophoblasts (3). However, whether integrin β3 participates in BMP2 signaling and mediates BMP2-increased human trophoblast invasion remains unknown.

The purpose of our study was to explore the effects of BMP2 on integrin αvβ3 expression and the possible mediation role of integrin β3 in BMP2-regulated human trophoblast invasion. We used immortalized human trophoblast cell line (HTR8/SVneo) and primary human extravillous trophoblast cells (EVTs) isolated from first-trimester villi as study models. RT-qPCR and Western blot assay were respectively utilized to detect the messenger RNA and protein levels of integrin αv and β3. The function of the target protein was studied by siRNA knockdown, and the trophoblast invasion ability was checked by Matrigel-coated transwell invasion assays. Our results demonstrated that the mRNA and protein levels of integrin β3, rather than integrin αv, were up-regulated after BMP2 treatment in HTR8/SVneo and primary EVT cells. Importantly, siRNA-mediated down-regulation of integrin β3 significantly inhibited basal and BMP2-induced HTR8/SVneo cell invasions measured by transwell invasion assay. In conclusion, we findings support that BMP2 promotes human trophoblast cell invasion by up-regulating integrin β3 expression, benefitting the in-depth understanding of the pro-invasive effect of BMP2 on human trophoblasts during early pregnancy. Reference: (1) Hong-Jin Zhao et al., Cell Death Dis 2018;9:174. (2) Damsky, C.H. et al, Development 1994; 120, 3657-3666. (3) Dong-Mei He et al., Reproduction 2019;157:423-430.

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Differential Expression Changes in Human Decidua With Term and Preterm Labor: Role for Upstream Targets in the Prostaglandin Pathway

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Introduction: Prostaglandins (PGs) are paracrine mediators thought to be important during pregnancy and labor. Synthesis of PGs is complex with three rate limiting steps, the second of which (PGTS2/cyclooxygenase) is a target for managing preterm labor, but this treatment is not always effective. It is suggested that alternate steps in the PG pathway may play distinct roles during labor and hence the potential as alternate targets for labor management.

The first step of PG synthesis involves the action of phospholipase A2 (PLA2) enzymes, of which over a dozen isotypes are known. However, PLA2 expression and role in the decidua (maternal-fetal interface) is unknown. We hypothesize that distinct PLA2 isotypes are present within the decidua and play a role in term and preterm labor. To this end, we conducted an expression profile of PLA2 subtypes and related PG genes within human decidua and determined differential expression patterns with labor at term and preterm. Methods: Decidual samples from term (40wks) and preterm (26-37wks) Cesarean deliveries, were used to assess PG gene expression by RNAseq and qRT-PCR (n=7 preterm non-labor, n=11 preterm labor, n=31 term non-labor, n=31 term labor). Analyses were conducted using student’s t-test and one-way ANOVA to compare labor (non-labor vs labor) or with gestation (preterm vs term) and adjusted for multiple testing using the Benjamini-Hochberg method. Results: RNAseq analysis identified 30 highly expressed PG genes in decidua, of which 12 had not been previously reported in the uterus, including 7 PLA2 isotypes. Confirming previous work, expression of PTG2S2 was higher with labor (p=0.011). In contrast, we demonstrate that PLA2 isotype expression is lower with labor, with further differences between term and preterm samples. With term labor, expression of PLA2 isotype 2D was lower compared to non-labor (p=0.047). Meanwhile, preterm labor was associated with lower expression of PLA2 isotype 16 (p=0.025) and 4C (p=0.026), compared to preterm non-labor. Expression of PLA2 subtypes 2A, 15 and 4A late was highest in late labor (p=0.016, 0.004, 0.03, respectively). Conclusion: The presence of multiple PLA2 subtypes within the decidua suggests the potential for fine tuning PG synthesis during pregnancy. Expression of PLA2 isotypes 16 and 4C was uniquely associated with preterm labor, suggesting these isotypes may play a role in the pathogenesis of preterm labor. Further investigation of the functional role of PLA2 isotypes may provide insight to a novel mechanism for preterm labor and identify potential targets for labor management.

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Effects of Dexamethasone on Offspring Survival and Intrauterine Growth Restriction

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The placenta is the primary organ responsible for deactivating maternal glucocorticoids and reducing fetal exposure. Glucocorticoid use during pregnancy is a common treatment for asthma, allergies, and COVID-19. Several studies have reported adverse effects including intrauterine growth restriction as a result of glucocorticoid exposure, yet little is known about the mechanisms by which short and long-term maternal glucocorticoid exposures affect placental biology and fetal development. To better understand the role of glucocorticoids on placental and fetal outcomes, we used a mouse model exposed