Association between Third Trimester Maternal Leptin, C-Peptide, Vascular Endothelial Growth Factor (VEGF), and Placental Growth Factor (PIGF) Levels and Development of Hypertensive Disorders of Pregnancy (HDOP) in Women with Type 2 Diabetes Mellitus (T2DM)

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Abstract

This study is to determine the association between maternal third trimester biomarker levels and development of hypertensive disorders of pregnancy (HDOP) among women with type 2-diabetes mellitus (T2DM). We performed a case-control study of data from a multicenter clinical trial of pregnant women with T2DM randomized to insulin plus metformin or insulin alone. Women had blood collected between 24 and 30 weeks' gestation as study protocol. Maternal serum leptin, c-peptide, VEGF, and PIGF levels were measured and our primary outcome was hypertensive disorder of pregnancy (HDOP) (gestational hypertension or pre-eclampsia). We determined the association between third trimester biomarkers, HDOP, delivery, and neonatal outcomes using t-test, chi-square, and logistic regression. We have data on 236 women, 84 (36%) cases and 152 (64%) controls. Compared to controls, cases were more frequently African American (44.1% vs. 29.6%, p=0.03) or had chronic hypertension (33.3% vs. 19.7%, p=0.02). Additionally, cases delivered earlier (mean 36.2 (SD 2.6) vs. 37.0 (SD 2.7) weeks, p=0.03) and were more likely to have 5 minute APGAR <7 (31% vs. 15.8%, p=0.006). Biomarkers were not different between cases and controls. In regression models, biomarkers were not associated with HDOP. Mothers of newborns requiring NICU admission or oxygen supplementation had higher leptin levels (p=0.005, p=0.004, respectively). C-Peptide levels were higher among mothers of neonates with 5 minute APGAR <7 (p=0.02). Thus, third trimester leptin and c-peptide levels may impact immediate neonatal birth outcomes, particularly respiratory drive. A larger sample size (n=352) would be powered to detect a leptin-mediated difference.

Keywords: type 2 diabetes mellitus, hypertensive disorders of pregnancy, leptin, c-peptide, VEGF, PIGF, biomarkers

Background

- People with overt Type 2 Diabetes Mellitus (T2DM) in pregnancy are at increased risk of hypertensive disorders (HDOP).
- Paucity of data to predict who will develop a HDOP and associated maternal or neonatal morbidity.
- Third trimester leptin, c-peptide, VEGF, and PIGF may be associated with HDOP severity and eventual clinical outcomes.

Objective

- To determine the association between maternal third trimester leptin, c-peptide, VEGF, and PIGF levels and HDOP among women with T2DM.

Methods

- Case control study of multicenter clinical trial of pregnant women with T2DM randomized to insulin plus metformin or insulin alone.

IINCLUSION CRITERIA	EXCLUSION CRITERIA
• Age 18-45 • Singleton non-anomalous pregnancy • Pre-existing T2DM or clinical diagnosis of diabetes between 10 weeks <20 weeks 6 days gestation	• Pre-existing renal disease (defined as creatinine > 1.5 mg/dL) • History of lactic acidosis • Allergy to metformin

- Blood sampled between 24 – 30 weeks, analytes measured using commercially available ELISA kits.
- HDOP defined as systolic BP > 140, diastolic BP > 90 at least 4 hours apart, presence of urine protein > 300 mg in 24 hours, and/or severe features.
- T-test, chi-square, and logistic regression used to determine association between maternal serum levels, HDOP, and pregnancy outcomes.

Results

- 236 women analyzed, 84 (36%) cases and 152 (64%) controls.
- Cases significantly more frequently identify as African American or have chronic hypertension.
- There was no significant difference between Leptin, c-peptide, VEGF, and PIGF levels between cases and controls.

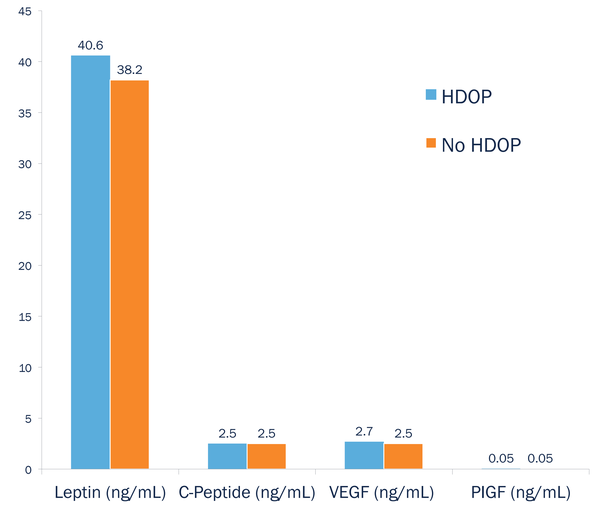
Results

Table 1. Demographic Characteristics

	HDOP (n=84)	No HDOP (n=152)	P-Value
Race			
Caucasian	27 (32.1)	65 (42.8)	0.11
African American	37 (44.1)	45 (29.6)	**0.03**
Gravidity	3 (2,5)	4 (3,5)	0.30
>1 Prior Preterm Birth	22 (26.2)	34 (22.4)	0.37
Pre-Pregnancy BMI	38.3 (8.8)	39.7 (25.2)	0.59
Married	52 (61.9)	105 (71.4)	0.14
Public Insurance	65 (77.4)	104 (68.4)	0.14
Chronic Hypertension	28 (33.3)	29 (19.7)	**0.02**

[a]Data presented as n(%) unless noted otherwise; Gravidity is noted as median (IQR); BMI shown as mean (SD).

Figure 1. Third trimester mean serum leptin, c-peptide, VEGF, and PIGF levels by primary outcome



Results

- Leptin levels significantly higher among mothers of neonates that required NICU admission or oxygen (p=0.005, p=0.004, respectively).
- C-Peptide levels significantly higher among mothers of neonates with 5 minute APGAR <7 (p=0.02).
- HDOP cases delivered at earlier mean gestational ages (36.2 (SD 2.6) vs. 37.0 (SD 2.7) weeks, p=0.03) and were more likely to have 5 minute APGAR <7 (31% vs. 15.8%, p=0.006).

Table 2. Mean third trimester analyte levels by neonatal outcomes

	Leptin (ng/mL)	C-Peptide (ng/mL)	VEGF (ng/mL)	PIGF (ng/mL)
< 37 weeks	43.8 (36.4)	2.5 (2.1)	2.7 (1.7)	0.04 (0.04)
Cesarean	42.4 (31.9)	2.5 (2.0)	2.7 (1.7)	0.05 (0.03)
Birthweight > 95%ile+	39.7 (24.1)	2.7 (2.1)	2.3 (1.3)	0.06 (0.03)
NICU admission	49.6(37.0)*	2.6 (2.4)	2.6 (1.6)	0.05 (0.03)
Oxygen Support	52.4 (37.3)*	2.3 (2.0)	2.8 (1.8)	0.04 (0.03)
Hypoglycemia	40.1(31.4)	2.6 (1.8)	2.6 (1.5)	0.04 (0.03)
APGAR < 7	36.0 (23.9)	1.5 (1.5)*	2.9 (1.9)	49.1 (31.3)

Data shown as mean (SD) unless noted otherwise;+Birthweight >95%ile is adjusted for gestational age at delivery; *Indicates p value < 0.05

Conclusions

In women with T2DM, elevated maternal third trimester leptin and C-peptide levels are associated with adverse neonatal outcomes. This suggests that in women with T2DM markers other than glucose reflect an adverse in-utero environment. Further research is needed to determine the clinical utility of leptin or C-peptide as predictors of neonatal outcome.

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