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)

Asha N. Talati,1 Amber Ivins,1 E. Nicole Teal,1 Kathleen Drexler,1 Karen F. Dorman,1 Nicole R. Wilson,1 Kim A Boggess1

1Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine
University of North Carolina School of Medicine and University of North Carolina Health Care, Chapel Hill, NC

Objectives

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

Methods

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 likely to have 5 minute APGAR <7 (31% vs. 15.8%, p=0.006) and were more likely to have 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).

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 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.
• Cases significantly more frequently identify as 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 at earlier mean (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 5 minute APGAR <7 (p=0.02).

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

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.

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.

Results

• Case control study of multicenter clinical trial of pregnant women with T2DM randomized to insulin plus metformin or insulin alone.
• 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 1. Demographic Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>HDOP (n=84)</th>
<th>No HDOP (n=152)</th>
<th>P-Value</th>
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</thead>
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<tr>
<td>Caucasian</td>
<td>27 (32.1)</td>
<td>65 (42.8)</td>
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<tr>
<td>African American</td>
<td>37 (44.1)</td>
<td>45 (29.6)</td>
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<td>Gravida</td>
<td>3 (2.5)</td>
<td>4 (3.5)</td>
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<td>&gt;1 Prior Preterm</td>
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<td></td>
<td></td>
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<tr>
<td>Birth</td>
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<tr>
<td>Pre-Pregnancy BMI</td>
<td>38.3 (8.8)</td>
<td>39.7 (25.2)</td>
<td>0.59</td>
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<tr>
<td>Married</td>
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<td>105 (71.4)</td>
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<tr>
<td>Public Insurance</td>
<td>65 (77.4)</td>
<td>104 (68.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Chronic Hypertension</td>
<td>28 (33.3)</td>
<td>29 (19.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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

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.