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Association between First Trimester Pregnancy Associated Plasma Protein–A (PAPP-A) and Gestational Diabetes Mellitus Development

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Background

◆ Affecting 5-6% of pregnancies, Gestational Diabetes (GDM) is a common pregnancy complication with significant cardiometabolic consequences for mothers and offspring.
◆ Previous research from our group suggests that adipose tissue IGFBP-5 and the metalloprotease PAPP-A (Pregnancy Associated Plasma Protein-A) may play a mechanistic role in GDM development by regulating functional IGF-1 levels and lipid storage and metabolism.

![Image: Conceptual framework of the role of adipose tissue and development of GDM](conceptual_framework.png)

Figure. In normal pregnancy, induction of IGFBP-5 increases the amount of sequestered IGF-1 and IGF-2 and PAPP-A degrades IGFBP-5 to release IGFs which in turn promote angiogenesis and hyperplastic expansion. In women with GDM, insufficient levels of IGFBP-5 and possibly decreased levels of PAPP-A, lead to decreased bioavailability of IGF which prevents proper angiogenesis resulting in adipocyte hypertrophy and decreased capillary density.

Methods

◆ Retrospective cohort from EMR data of 1,251 women delivering singleton gestations during the years 2009, 2010, 2014 and 2015
◆ PAPP-A was measured in the first trimester (11-14 weeks) as part of routine aneuploidy screen, and reported as quartiles of multiples of the mean (MoM) based on gestational age and adjusted for maternal weight and race/ethnicity.
◆ GDM diagnosis was based on a standard 2-step protocol (~24-28 weeks; failed 50g 1hr glucola screen followed by ≥2 abnormal values per Carpenter-Coustan criteria on 100g 3hr glucose tolerance test).
◆ Crude and multivariable-adjusted logistic regression models estimated the association between PAPP-A MoM quartiles and GDM.

![Image: Table showing odds ratios and confidence intervals](odds_ratios.png)

Figure: Incident gestational diabetes mellitus (GDM) in relation to first-trimester PAPP-A, pre-pregnancy BMI, and age, OR (95% CI)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ref)</td>
<td>1.00</td>
<td>1.00 - 1.00</td>
<td>0.72</td>
</tr>
<tr>
<td>2</td>
<td>0.48</td>
<td>0.26 - 0.88</td>
<td>0.0006</td>
</tr>
<tr>
<td>3</td>
<td>0.55</td>
<td>0.30 - 0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.27</td>
<td>0.13 - 0.53</td>
<td>0.00</td>
</tr>
</tbody>
</table>

◆ Adjusting for pre-pregnancy BMI, nuchal transluency, crown rump length, smoking status, and parity, women with PAPP-A MoM 1st quartile had 52% (OR=0.48, 95%CI=0.26-0.88), 45% (OR=0.55, 95%CI=0.30-0.99) and 73% (OR=0.27, 95%CI=0.13-0.53) lower odds of developing GDM vs women in the 1st quartile.

Results

- 7.6% (n=95) of women developed GDM.
- Median PAPP-A MoM levels were 0.7 (interquartile range [IQR]=0.5-1.0) among women with GDM & 0.9 (IQR=0.6-1.3) among women who did not develop GDM.

Conclusions

◆ Higher PAPP-A MoM levels were associated with lower GDM risk.
◆ Future studies should assess whether higher PAPP-A levels are associated with enhanced IGF-1 signaling and improved pregnancy metabolic homeostasis.

Acknowledgements

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