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

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Pregnancy Associated Plasma Protein, PAPP-A, Gestional diabetes mellitus, IGFBP-5, IGF-1

Comments
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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 (**P**regnancy **A**ssociated **P**lasma **P**rotein-A) may play a mechanistic role in GDM development by regulating functional IGF-1 levels and lipid storage and metabolism.

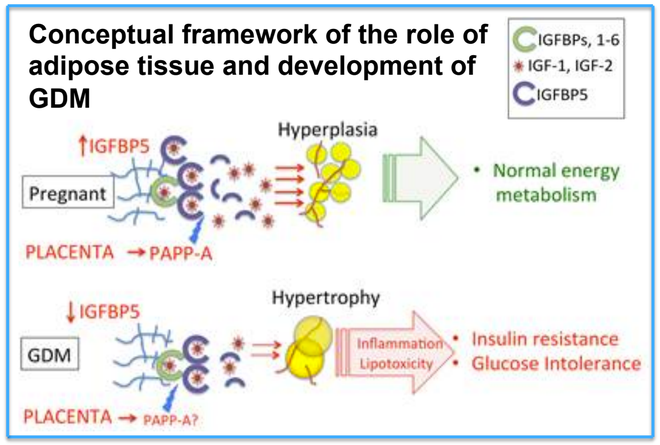


Figure. In normal pregnancy, induction of IGFBP-5 increases the amount of sequestered IGF-1 and IGF-2 and PAPP-A degrades IGFBP-5 to release IGFs which in turn promote angiogenesis and hyperplastic expansion. In women with GDM, insufficient levels of IGFBP-5 and possibly decreased levels of PAPP-A, lead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

Objective

To examine the relationship between circulating PAPP-A levels and GDM development. We hypothesized that high first trimester PAPP-A levels would be associated with decreased GDM risk.

Methods

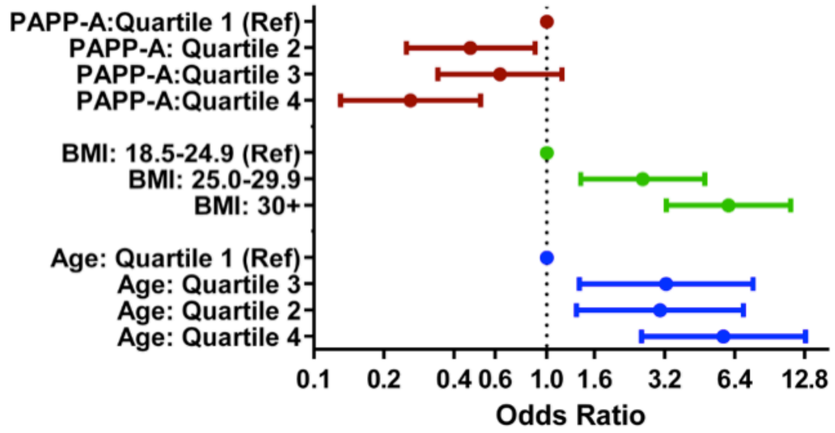
- Retrospective cohort from EMR data of 1,251 women delivering singleton gestations during the years 2009, 2010, 2014 and 2015
- PAPP-A was measured in the first trimester (11-14 weeks) as part of routine aneuploidy screen, and reported as quartiles of multiples of the mean (MoM) based on gestational 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.

Results

	Normal (N=1,156)	GDM (N=95)
	N	N
Age at lab visit (mean, SD)	29.5 (5.7)	32.4 (5.0)
Gestational age at lab visit (mean, SD)	12.5 (0.6)	12.4 (0.5)
Pre-Pregnancy BMI		
Normal weight	615 (53%)	24 (25%)
Overweight	317 (27%)	32 (34%)
Obese	224 (19%)	39 (41%)
Cigarette smoker		
No	1019 (88%)	87 (91%)
Smoker	76 (7%)	2 (2%)
Parity		
Nulliparous	473 (41%)	26 (27%)
Multiparous	683 (59%)	69 (73%)
Crown Rump Length (median, p25,p75)	1.3 (1.1, 1.6)	1.3 (1.1, 1.7)
Nuchal Transulency (median, p25,p75)	6.5 (5.7, 55.7)	6.4 (5.6, 50.5)

- 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.

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



- Adjusting for pre-pregnancy BMI, nuchal translucency, crown rump length, smoking status, and parity, women with PAPP-A MoM in 2nd, 3rd, and 4th quartiles 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.

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.

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