Metabolic Phenotypes in Maternal Obesity that Contribute to Higher Birthweight

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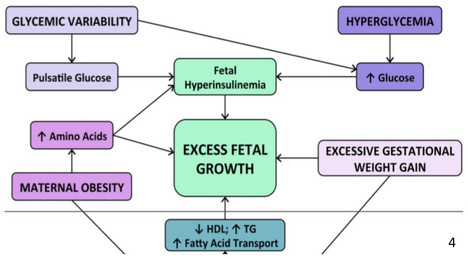
BACKGROUND

Pregnancies complicated by maternal obesity result in 10-15% babies to be born large for gestational age (LGA) [1]. These infants have significant birth related traumas, and a higher long-term risk for developing metabolic and neurological diseases[2]. However, most obese mothers give birth to appropriate for gestational age babies (AGA). Currently, the mechanisms that lead to accelerated fetal growth remain unclear[1].

In the obese pregnant population, it has been reported that levels of insulin, leptin and inflammatory cytokines are increased, and adiponectin is decreased, compared to normal body mass index (BMI) population[3]. These factors influence maternal metabolism, but their role in modulating the growth of the fetus in obese mothers is not clear.

We hypothesize that metabolic hormones and inflammatory cytokines contribute to accelerated fetal growth in obese mothers resulting in LGA neonates.



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METHODS

1) Maternal and umbilical cord plasma and placentas were collected from obese women that delivered AGA (n=21) or LGA (n=30) infants.
2) Using ELISA, concentrations of insulin, leptin and adiponectin were determined in maternal venous and umbilical cord plasma.
3) Colorimetric assay was used to measure maternal triglycerides.
4) Multiplex sandwich assay tested additional markers including glucagon like peptide-1 (GLP-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), vascular endothelial growth factor- A and D (VEGF-A, VEGF-D), placental growth factor (PIGF) and FMS-like tyrosine kinase 3 ligand (Flt3L).
5) Unpaired T-tests and Pearson Correlation coefficients were used to analyze results.
6) GLP-1R was identified in the syncytiotrophoblast microvillous membrane (MVM) by immunoblot and by immunohistochemistry.

RESULTS

Maternal Plasma:

- Triglyceride levels were higher in LGA males than AGA males (**Figure 1**).
- Maternal GLP-1 levels were higher in LGA pregnancies compared to AGA births ($p<0.05$). GLP-1 levels also positively correlated to higher birthweights in both cohorts **(Figure 2).**
- No significant differences in LGA and AGA pregnancies for concentrations of insulin, leptin, adiponectin, IL-6, TNF-α, PIGF, VEGF-A, VEGF-D, or FLt3L.

Umbilical Cord Plasma:

- Insulin levels were insignificantly increased in LGA infants compared to AGA ($p<0.05$) (**Figure 3).**
- GLP-1 levels were higher in LGA compared to AGA neonates.

Placenta:

- Localization of GLP-1R in the syncytiotrophoblast microvillous membrane (MVM) **(Figure 4).**

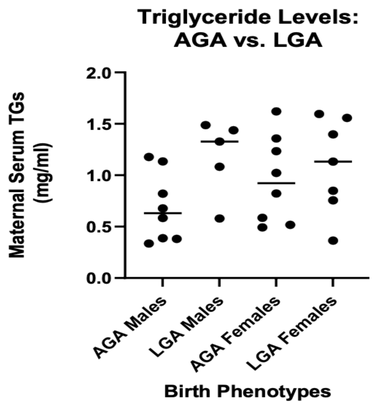


Figure 1. Triglyceride levels in LGA males are higher than AGA males ($P<0.05$).

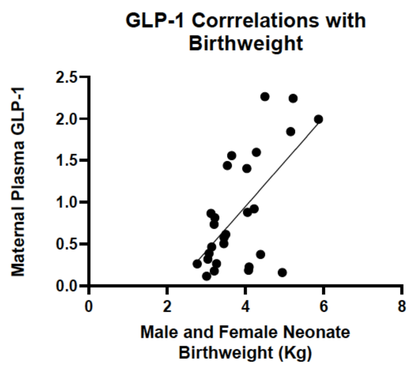


Figure 2. GLP-1 levels have a positive correlation with birthweight ($P<0.05$).

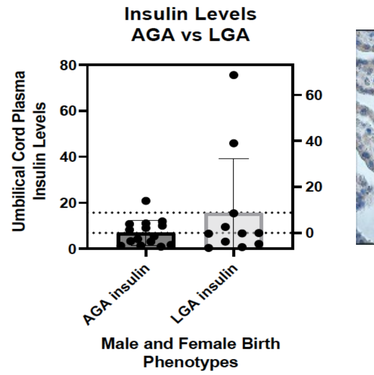


Figure 3. Insulin levels are insignificantly higher in LGA compared to AGA infants $P>0.05$).

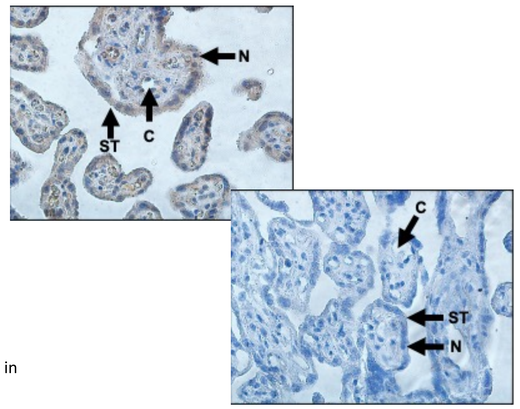
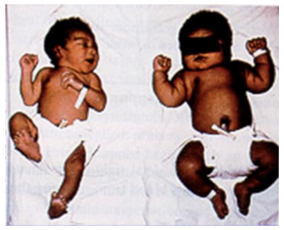


Figure 4. GLP1-R identified on MVM through IHC. Fetal capillary (C), syncytiotrophoblast (ST), nucleus (N). *Photos taken by Jerad Dumolt

CONCLUSIONS

We identified, for the first time, increased maternal plasma GLP-1 as a strong correlate with accelerated fetal growth in pregnancies complicated by maternal obesity **(Figure 2).** We also localized the GLP-1 receptor to the syncytiotrophoblast MVM with immunohistochemistry (IHC) **(Figure 4).** This data suggests that maternal GLP-1 levels influence placenta function to increase nutrient flux to the fetus, accelerating fetal growth.

We speculate that higher fetal insulin in the LGA cord blood **(Figure 3)** may be related to higher fetal GLP-1 levels which contributes to fetal insulin resistance; however, the exact mechanism remains unknown.



Picture 1. AGA versus LGA baby of same gestational age[5].

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