Maternal hyperglycemia and its effects on placental vascular tone and endothelial nitric oxide activity

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Placenta = Greek root; *plakuos*

**Diogenes of Apollonia, 400BC**
First to theorize that placentas nourish the developing baby… by direct suckling

**Aristotle, 384BC**
Recognized role of the umbilical cord in placenta nutrient flow

**Gabriel Fallopius, 1523**
Systematically characterized female reproduction… named the placenta!

**Francois Mauriceau, 1637**
Publications facilitated the science of obstetrics
Placentas role in fetal nutrition

• Interface for gas exchange and metabolites

• Source of maternal plasma cytokines and hormones $^{1-2}$

• Conducts lipid synthesis/catabolism $^3$

• Complications linked to placental metabolism
  • Preenclampsia
  • Gestational Diabetes Mellitus

Gestational Diabetes Mellitus

- Frequency 17.8% worldwide (HAPO study 2011)¹
  - Lowest frequency Israel, greatest U.S.
- Risk factors include: Obesity, age >30, family history, race²
  - >46% GDM associated with excessive BMI
- Associated with several pregnancy adverse outcomes¹
  - Pre-eclampsia
  - Postpartum hemorrhage
  - Stillbirth
  - Macrosomia
  - Fetal hypoglycemia
- Elevated risk for maternal and fetal type II diabetes and dyslipidemia³
- Characterized by hyperglycemia from insulin resistance⁴
  - Diagnosed 2nd or 3rd trimester
  - Typically clears following birth

Hyperglycemia and pregnancy

- Insulin sensitivity decreases with normal pregnancies
  - GDM significantly lower
  - Imbalance of maternal glucose uptake
- Associated with placental vascular dysfunction and altered vascular tone
- Vascular dysfunction central to adverse outcomes
  - Cause or consequence?
  - Well characterized for adult onset type II diabetes
  - For GDM/placenta experimental evidence limited

2. Leach L. J Anat. 2009. PMID 195635533
Ex Vivo Placenta Dual Perfusion Model

Dual Perfusion and Dual Cotyledon Model

Dr. Luckey Reed
Experimental Design

Hypothesis:

Hyperglycemia alters the placental vascular resistance by invoking molecular changes in tone signaling.
Normal Placental Response to hyperglycemia

- **Graph:**
  - X-axis: Time points (Baseline, Post treatment, THX, 1 min, 2 min, 3 min, 4 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min).
  - Y-axis: Pressure in mmHg.
  - Two lines: Control 100mg/dL and Hyperglycemic 300mg/dL.
  - Asterisks (*) indicate significance at p<0.05 by student's t-test.

- **Images:**
  - Pre-perfusion, Post-perfusion 100mg/dL, Post-perfusion 300mg/dL.
  - Labels: Endothelium and stroma, Smooth Muscle, Nuclei.
Molecular mechanism of altered tone

• Nitric oxide (NO) is a principle vasodilator
• Alterations in synthesis implicated in many vascular diseases
  - preeclampsia, HTN, atherosclerosis, Type II diabetes
• eNOS activity regulated by phosphorylation of serine 1177 residue
  - perturbed in Type II diabetes (PMID 23264539, 16731827)
Hyperglycemic influence on eNOS activity

Western blot quantification (phospho / total eNOS)

Pre-perfusion

Control

Hyperglycemia

P-eNOS (Ser1177)

Total eNOS

Sample number

P = 0.025

P = 0.029
Normal vs. GDM eNOS activity

Phospho-eNOS (Ser1177)
Total eNOS
Sample number

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Bar graph showing the relative density of phospho-eNOS (Ser1177) in normal and GDM samples. The graph indicates a statistically non-significant difference (NS) between the two groups.

Legend:
- NS: Statistically non-significant
Conclusion

- Hyperglycemia alters the pressure response of normal placental arteries

- Results suggest an imbalance of constriction-dilation pathways

- Correlated with reduced activation of eNOS indicated by ser1177 phosphorylation
  - Hyperglycemia alone invokes perturbation
  - Similar baseline phosphorylation in managed GDM vs. normal placentas
  - Is eNOS activity perturbed due to uncoupling?

- Signaling cascade of hyperglycemia currently under investigation
  - How elevated glucose directly or indirectly invoke signaling
  - Akt and PKA-C perturbation
  - Osmotic effects of hyperglycemia
Acknowledgments

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Questions?

Oh no!