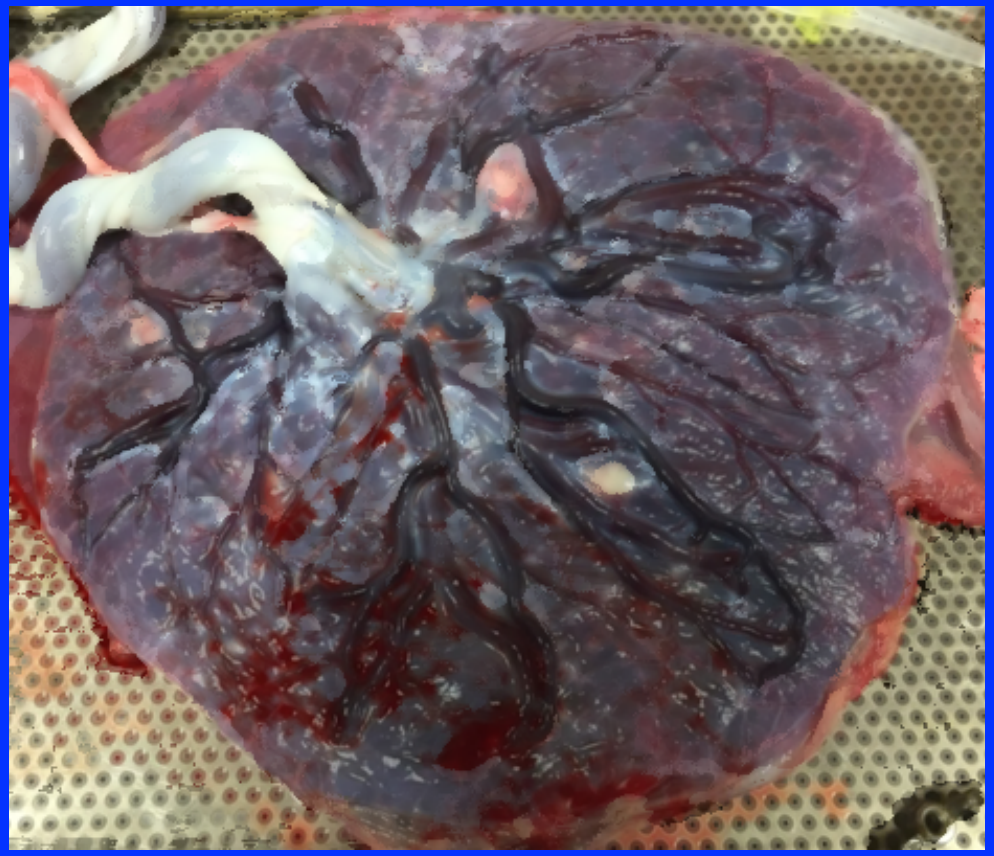
Maternal hyperglycemia and its effects on placental vascular tone and endothelial nitric oxide activity



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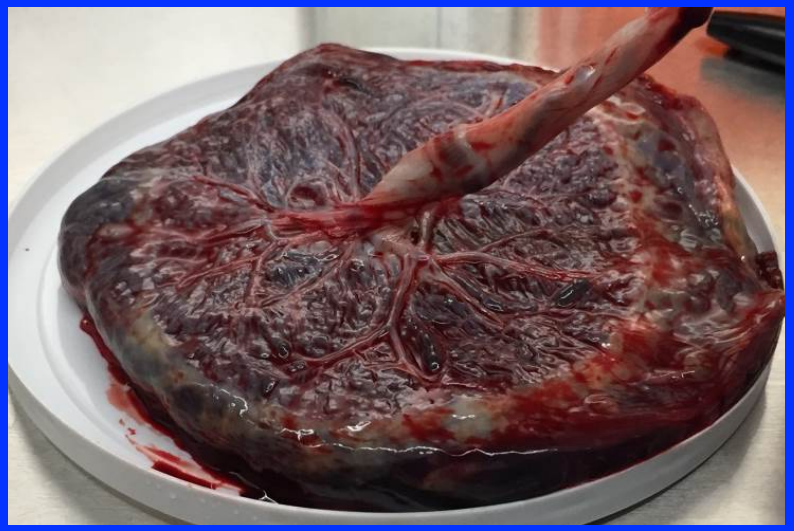
Placenta = Greek root; *plakuos*



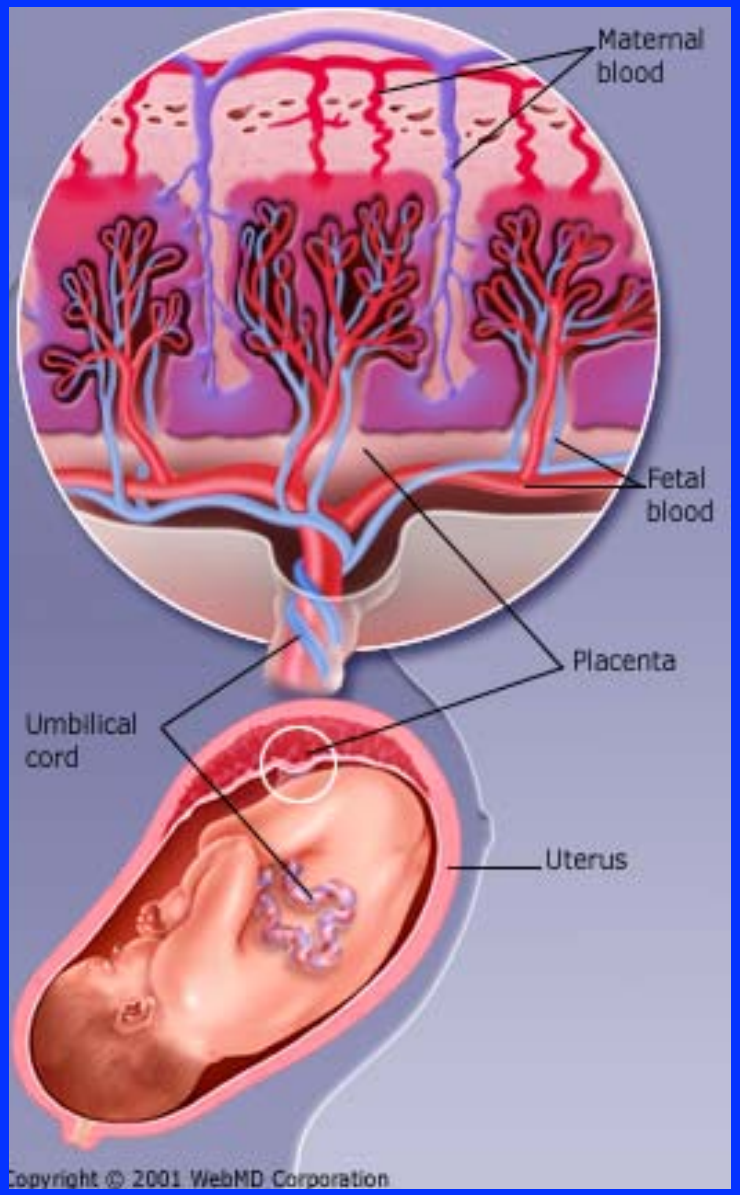
Diogenes of Apollonia, 400BC
First to theorize that placentas nourish the developing baby… by direct suckling

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 Mellites**

1. Desoye . And Haugel-de Mouzon S. Diabetes Care. 2007. PMID 17596459.
2. Brett KE et al. int J Mol Sci. 2014. PMID 25222554.
3. Dsoye G. et al. Am J of Clin Nutr. 2011. PMID 21543540.

Gestational Diabetes Mellites

- Frequency 17.8% worldwide (HAPO study 2011) [1]
  - Lowest frequency Israel, greatest U.S.
- Risk factors include: Obesity, age >30, family history, race [2]
  - >46% GDM associated with excessive BMI
- Associated with several pregnancy adverse outcomes [1]
  - Preenclampsia
  - Postpartum hemorrhage
  - Stillbirth
  - Macrosomia
  - Fetal hypoglycemia
- Elevated risk for maternal and fetal type II diabetes and dyslipidemia [3]
- Characterized by hyperglycemia from insulin resistance [4]
  - Diagnosed 2nd or 3rd trimester
  - Typically clears following birth

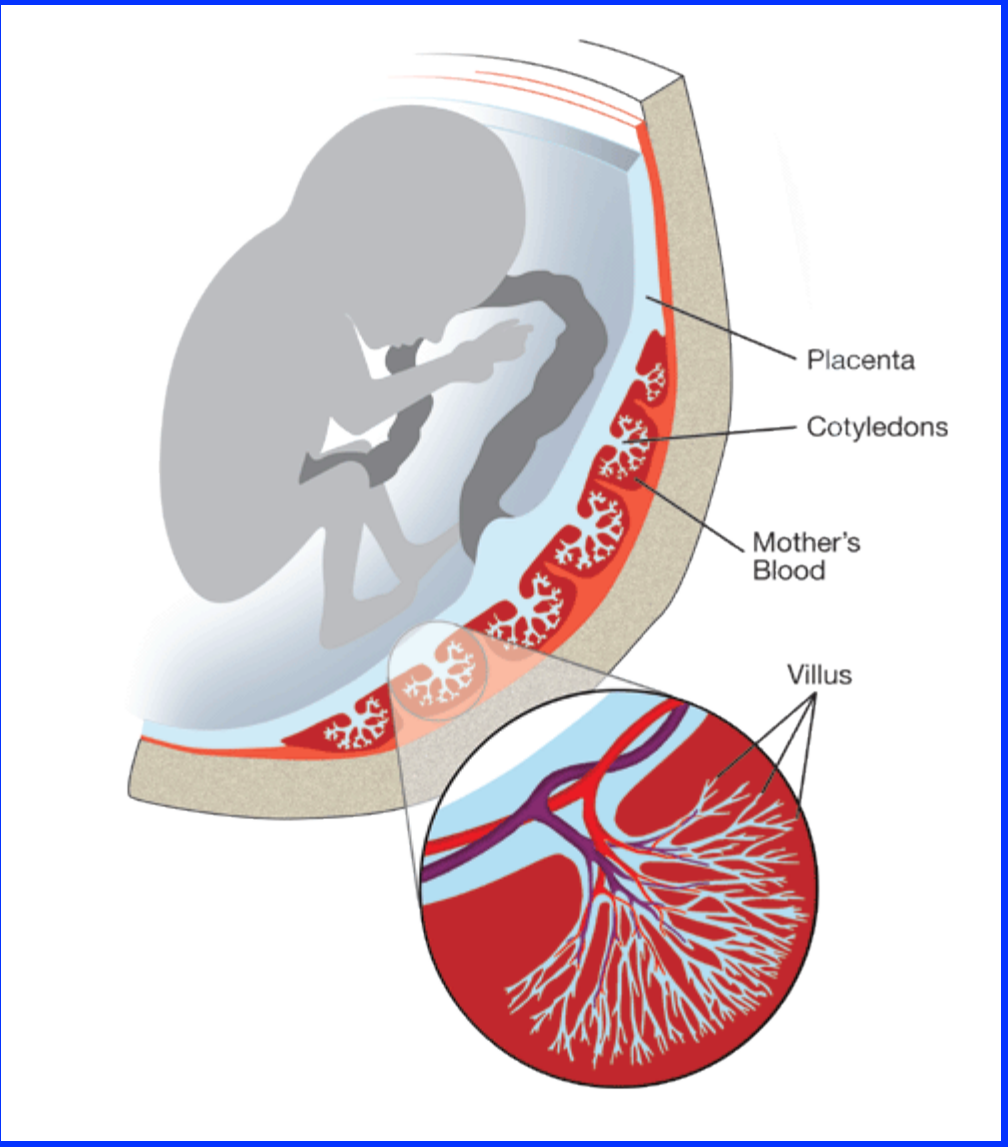
1. Sacks DA et al. Diabetes Care. 2012. PMID 22355019
2. Kim SY et al. Am J Public Health. 2010. PMID 20395581
3. Yessoufou A. and Motairou K. Exp Diabetes Res. 2011. PMID 22144985
4. Buchanan T. and Xiang H. JCI. 2005. PMID 15765129

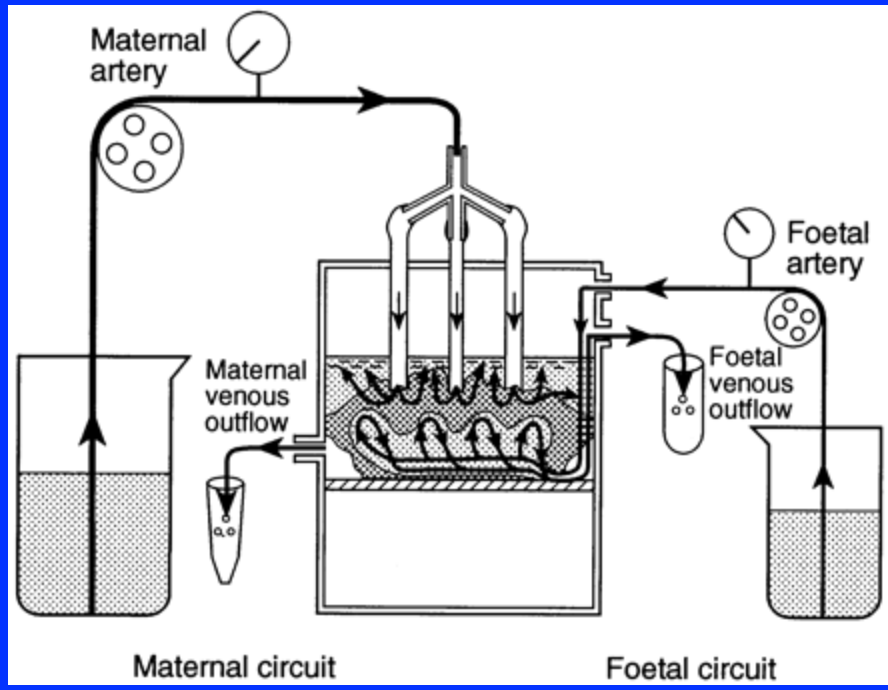
Hyperglycemia and pregnancy

- Insulin sensitivity decreases with normal pregnancies [1]
  - GDM significantly lower
  - Imbalance of maternal glucose uptake
- Associated with placental vascular dysfunction and altered vascular tone
- Vascular dysfunction central to adverse outcomes [2]
  - Cause or consequence?
  - Well characterized for adult onset type II diabetes
  - For GDM/placenta experimental evidence limited

1. Catalano PM et al. Am J Obstet Gynecol. 1999. PMID 10203659.
2. Leach L. J Anat. 2009. PMID 195635533

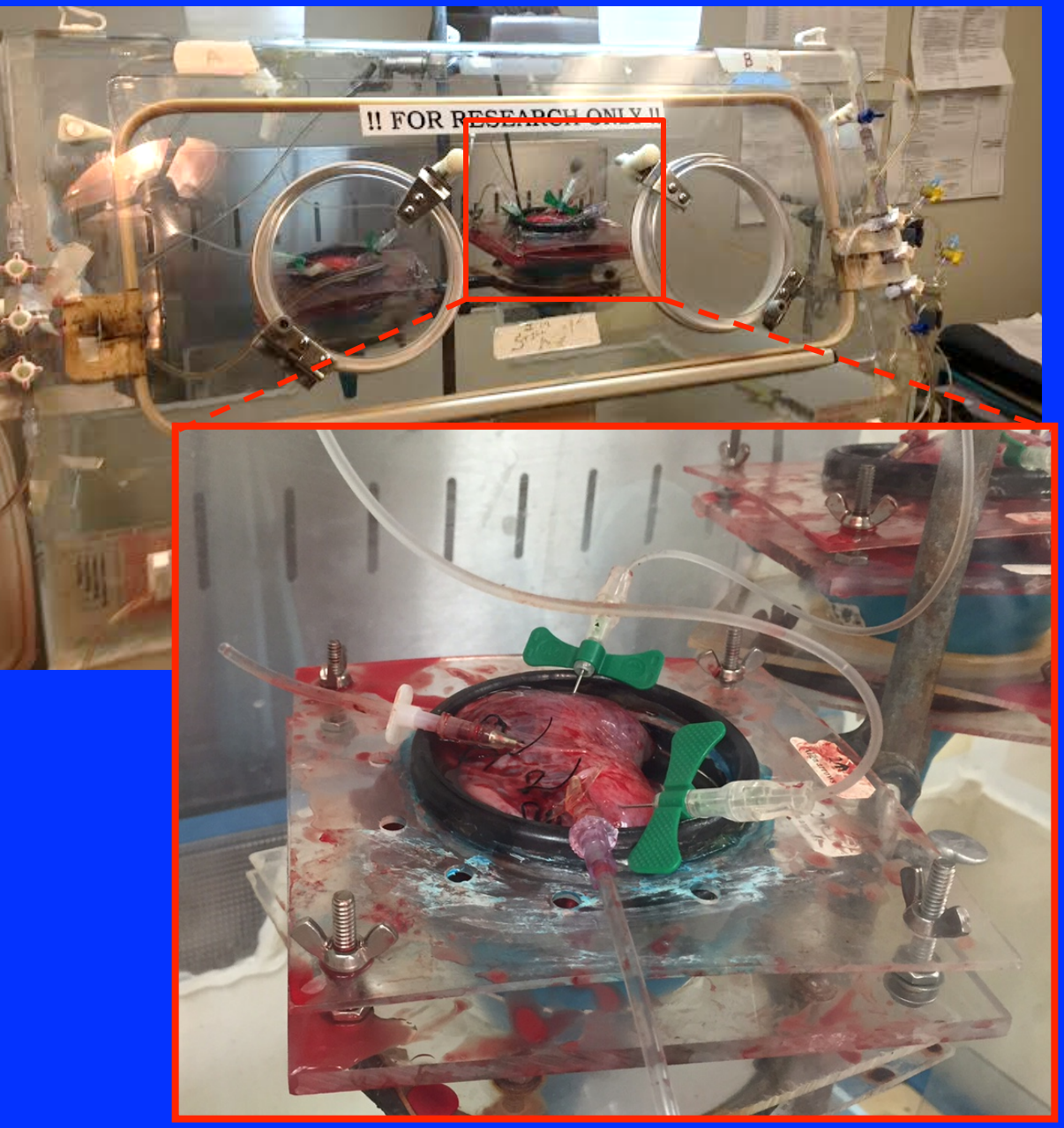
Ex Vivo Placenta Dual Perfusion Model

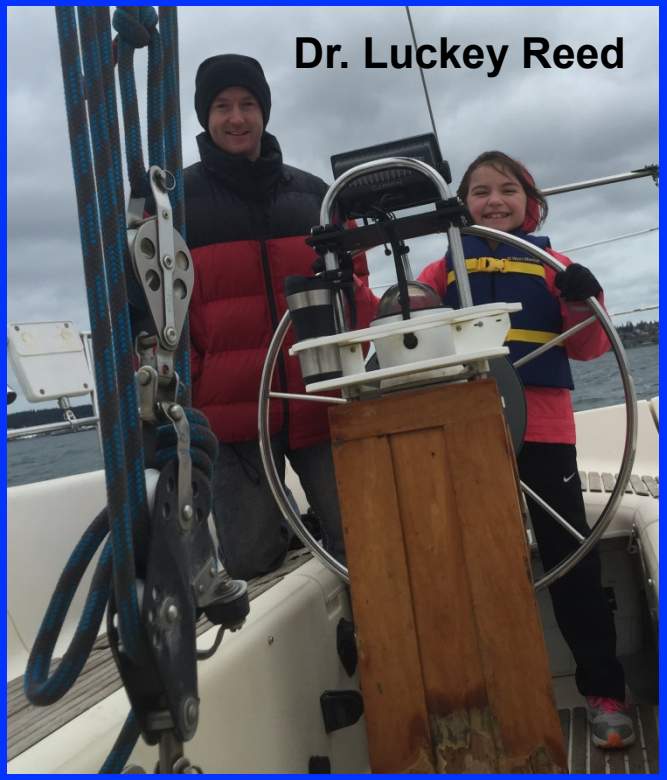




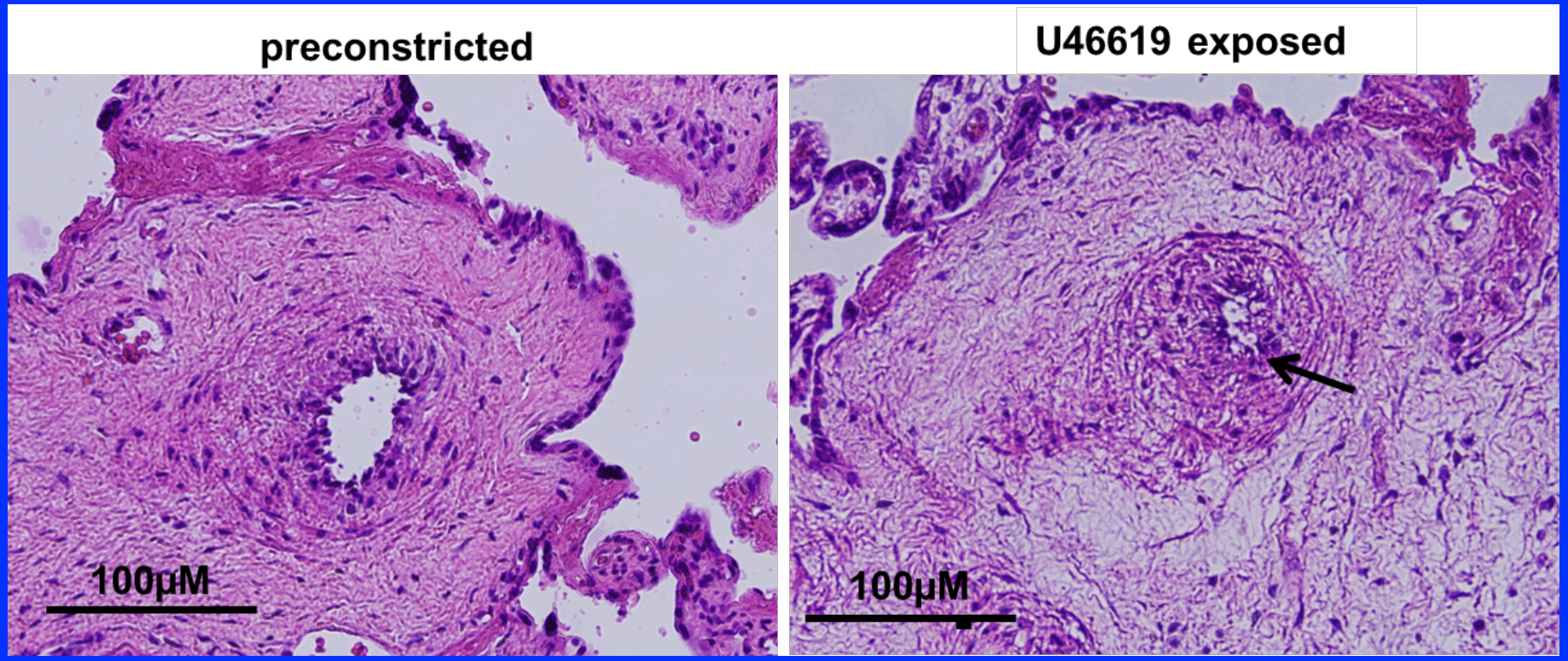
He YL. et al. . et al. Br J Anaesth. 2000. PMID 10992839.

Dual Perfusion and Dual Cotyledon Model





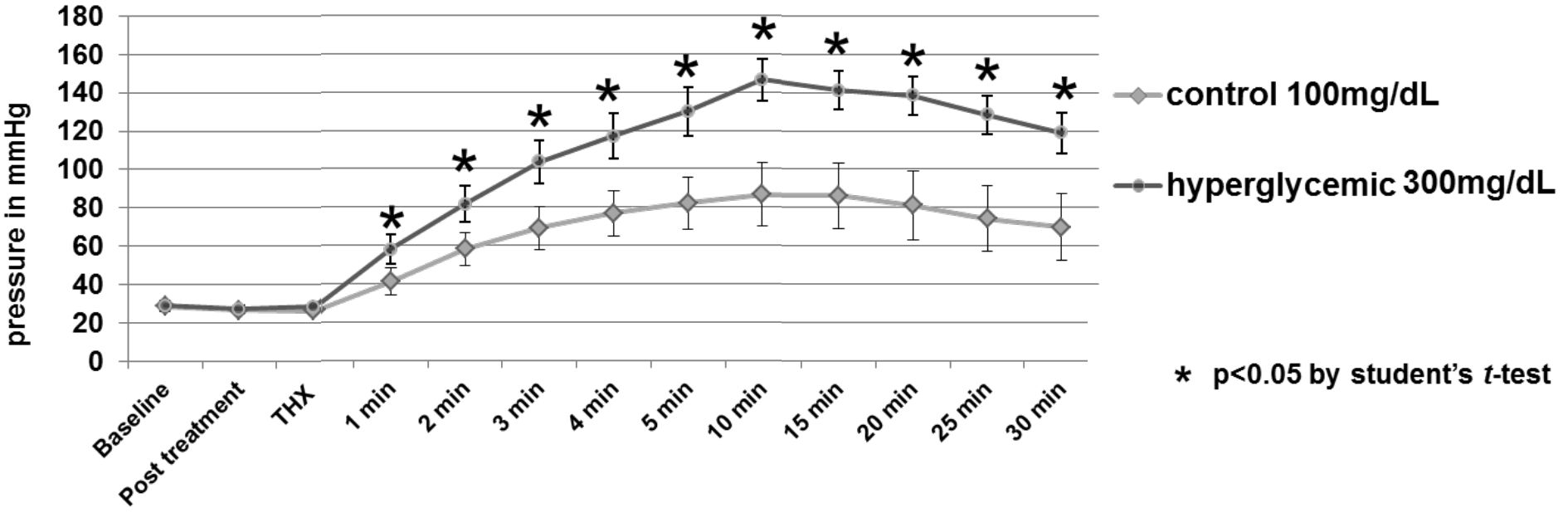
Experimental Design

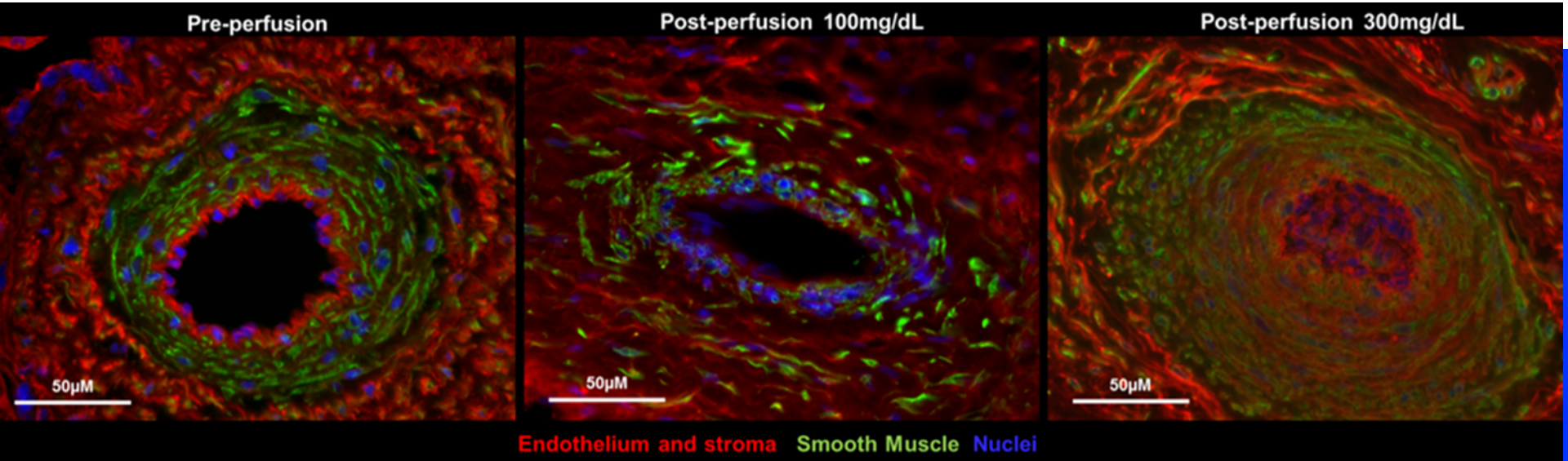


Hypothesis:

Hyperglycemia alters the placental vascular resistance by invoking molecular changes in tone signaling

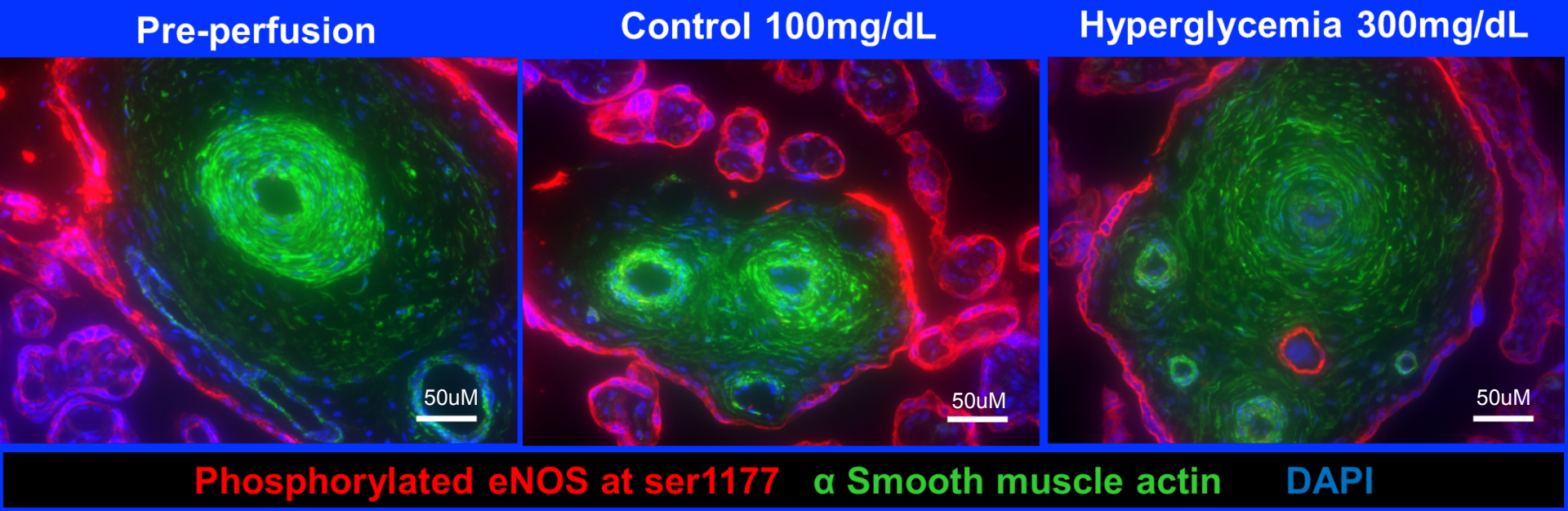
Normal Placental Response to hyperglycemia



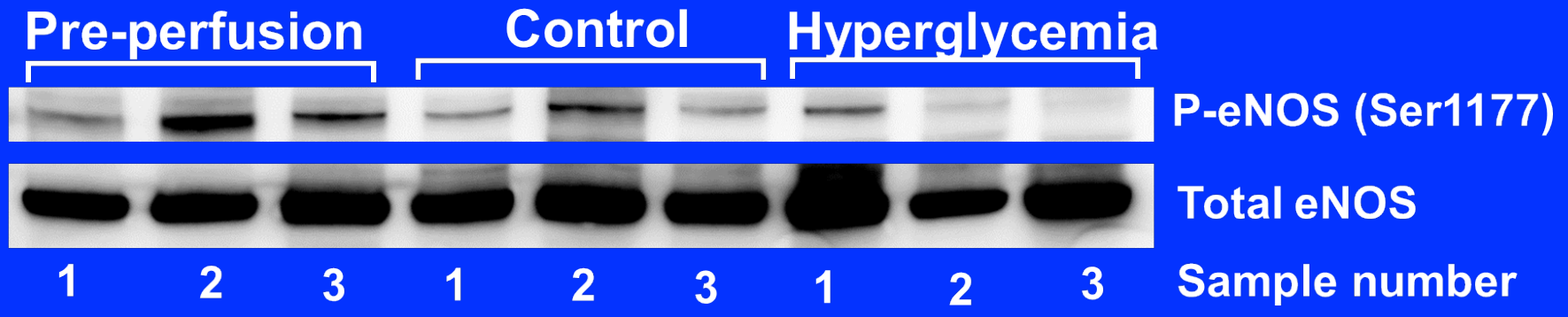


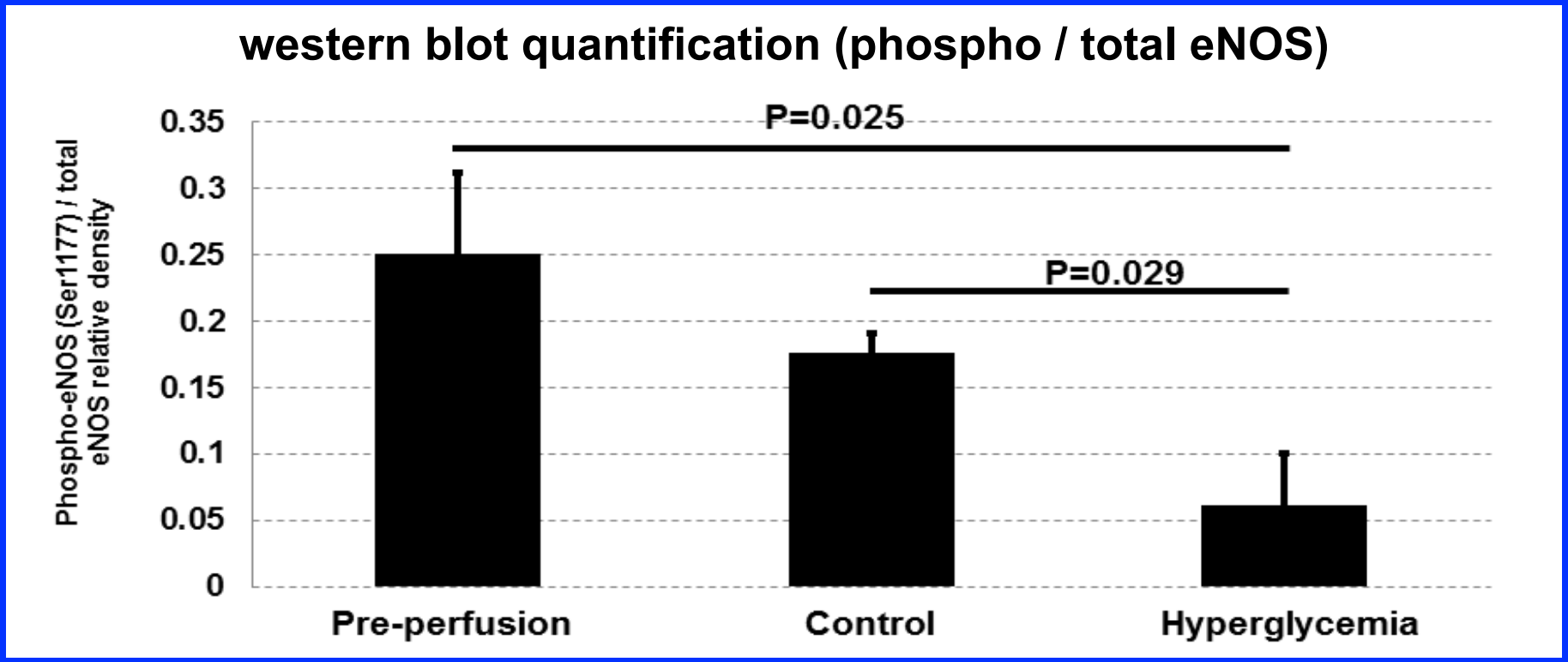
Molecular mechanism of altered tone

- 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)

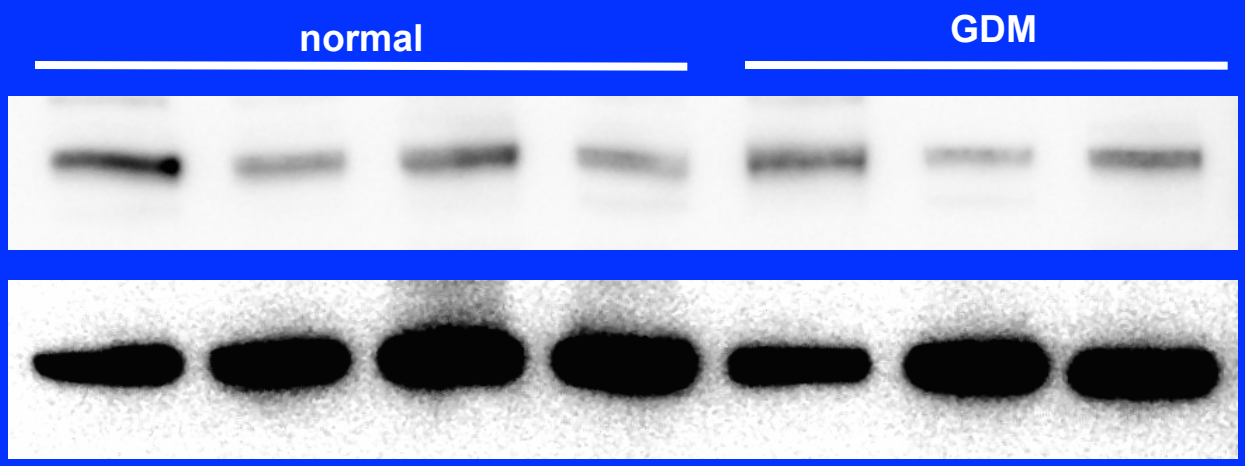


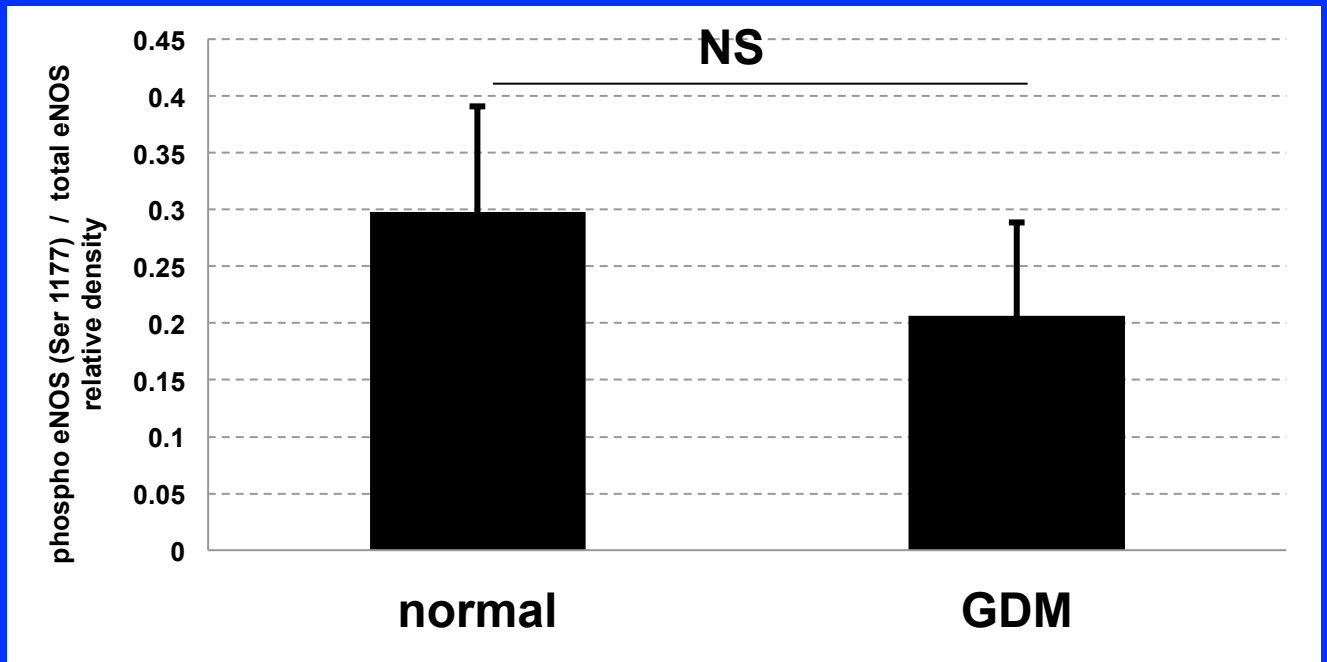
Hyperglycemic influence on eNOS activity





Normal vs. GDM eNOS activity





Conclusion

- Hyperglycemia alters the pressure response of normal placental arteries
- Results suggests an imbalance of constriction-dilation pathways
- Correlated with reduced activation of eNOS indicated by ser1177 phosphorylation
  - Hyperglycemia alone invokes perturbation
  - Similar baseline phosphorylation in 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?