Maternofetal inflammation at mid-gestation impairs subsequent fetal growth, insulin secretion, and muscle-specific glucose metabolism

Zena M. Hicks, Rachel L. Gibbs, Haley N. Beer, Pablo C. Grijalva, Micah S. Most, and Dustin T. Yates

Stress Physiology Laboratory, Department of Animal Science, University of Nebraska-Lincoln, Lincoln, NE, USA

Abstract

Objectives: Maternofetal inflammation at 0.7 gestation causes intrauterine growth restriction (**IUGR**) in fetal sheep. However, inflammation during peak placental development has not been explored. Therefore, we determined the effects of maternofetal inflammation at 0.5 gestation on fetal glucose metabolism and insulin secretion near term.

Methods: Pregnant ewes were injected every 3rd day from d50 to 65 of gestation (term=d150) with saline (controls; n=11) or lipopolysaccharide to induce maternofetal inflammation and IUGR (**MI-IUGR**; n=11). Fetuses were catheterized on d118. Hyperglycemic clamps and hyperinsulinemic-euglycemic clamps were performed on d123 and 124, respectively. Fetuses were necropsied at d125.

Results: Basal plasma insulin did not differ between control and MI-IUGR fetuses, but glucose-stimulated insulin secretion was less ($P<0.05$) for MI-IUGR fetuses. Blood HCO_3, hemoglobin, Na^+, and K^+ were less ($P<0.05$) for MI-IUGR fetuses regardless of period, but blood glucose and lactate did not differ. Fetal hindlimb glucose uptake did not differ between groups at basal or hyperinsulinemia. Hindlimb glucose oxidation was less ($P<0.05$) for MI-IUGR fetuses, regardless of period. Plasma insulin and blood glucose did not differ between groups, but glucose-to-insulin ratios were greater ($P<0.05$) for MI-IUGR fetuses than controls under basal conditions. Blood O_2 was ~14% less ($P<0.05$) for MI-IUGR fetuses than controls, regardless of condition. At necropsy, MI-IUGR fetuses were 20% lighter ($P<0.05$) and their cannon bones were 6% shorter ($P<0.05$) than controls. MI-IUGR fetuses had smaller ($P<0.05$) hindlimbs and *semitendinosus*, *flexor digitorum superficialis*, *longissimus dorsi* muscles. Fetal heart, brain, liver, and kidney masses did not differ between groups.

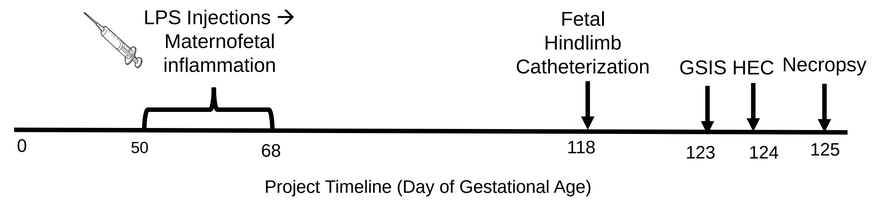
Conclusion: Maternofetal inflammation during peak placental development led to fetal hypoxemia but not hypoglycemia in later gestation. This coincided with poor β cell function, impaired hindlimb glucose oxidative capacity, and fetal growth restriction. These findings reflect metabolic phenotypes observed for other IUGR models and indicate some degree of placental insufficiency.

Introduction

What we already know → Late Gestation Maternofetal Stress → **IUGR**

What we still want to know → Mid-Gestation Maternofetal Stress → *Placental Insufficiency?* → **IUGR**

Methods



Conclusions

Maternofetal inflammation during peak placental development

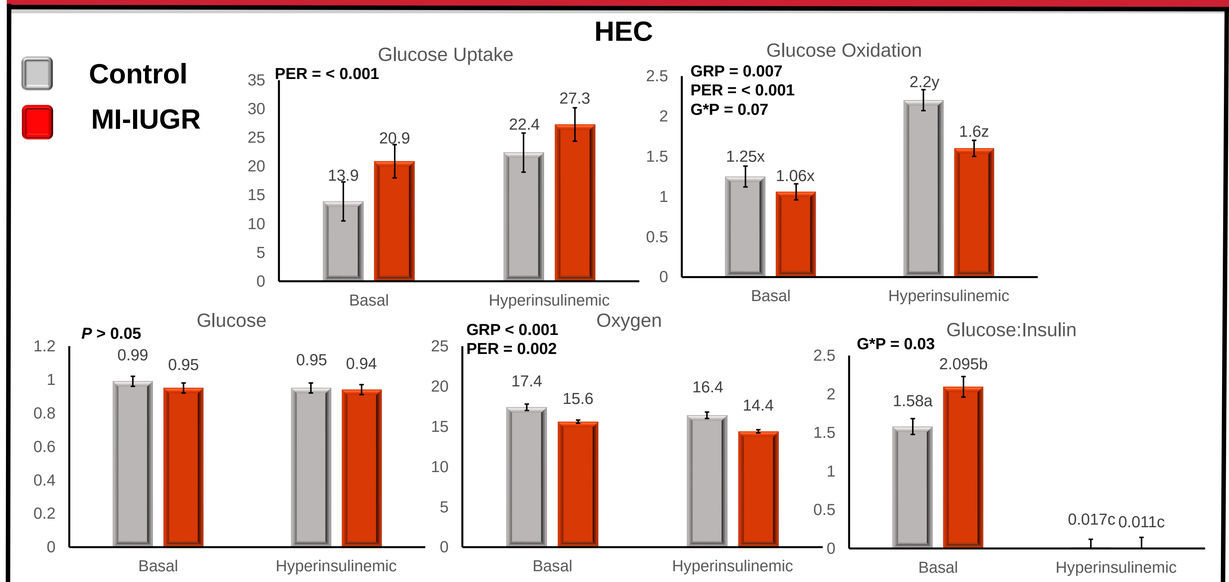
↓

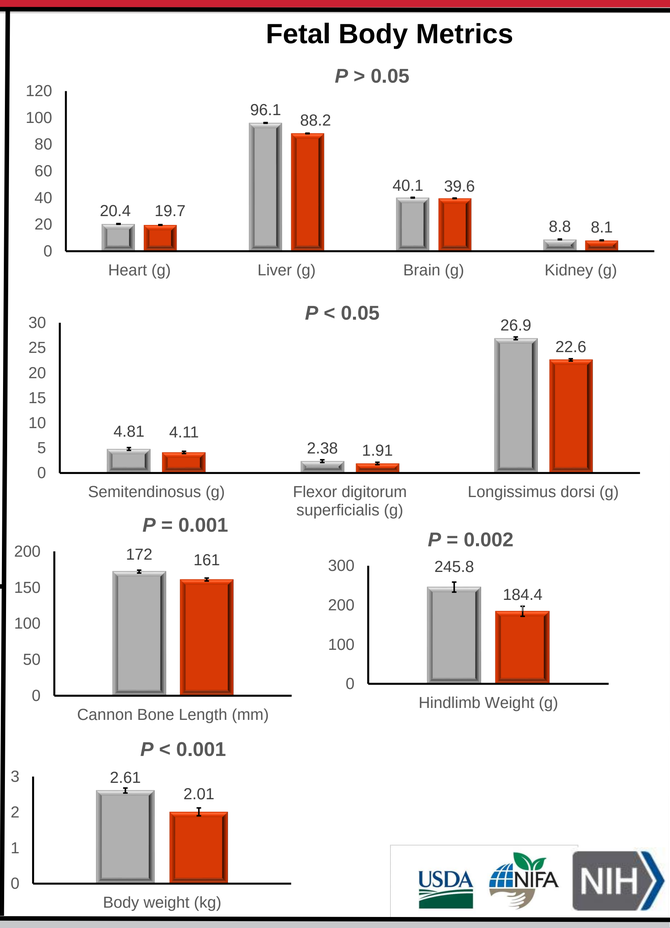
Fetal *hypoxemia*
NOT *hypoglycemia*

→ ↓ β-cell function
↓ Hindlimb glucose oxidation
Fetal Growth Restriction

→ Similar **metabolic phenotype** of other IUGR models
At least ***partial placental insufficiency***

Results





USDA NIFA NIH

IN OUR GRIT, OUR GLORY.