FETAL HYPERGLYCEMIA AND HYPERINSULINEMIA PROGRAM TISSUE-SPECIFIC POSTNATAL INSULIN RESISTANCE

Kok Lim Kua, MD
Neonatal-Perinatal Medicine Fellow
Stead Family Department of Pediatrics
University of Iowa Children’s Hospital
Disclosure

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity

• I DO NOT intend to discuss an unapproved/investigative use of a commercial product/device in my presentation
INCREASED RISK OF INSULIN RESISTANCE STATES IN OFFSPRING

<table>
<thead>
<tr>
<th>Maternal Condition</th>
<th>Offspring Outcome</th>
<th>Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>T2DM</td>
<td>OR - 3.7</td>
<td>Dabelea 2000</td>
</tr>
<tr>
<td>Gest IGTT</td>
<td>T2DM</td>
<td>Risk 51% vs 8%</td>
<td>Franks 2006</td>
</tr>
<tr>
<td>GDM/T1DM</td>
<td>Prediabetes/T2DM</td>
<td>OR 7.76</td>
<td>Clausen 2008</td>
</tr>
<tr>
<td>DM/Obesity</td>
<td>T2DM</td>
<td>OR 3.9</td>
<td>Dabelea 2008</td>
</tr>
<tr>
<td>GDM</td>
<td>Obese/MetSyn</td>
<td>OR obese 2/MetSyn4</td>
<td>Clausen 2009</td>
</tr>
<tr>
<td>GDM</td>
<td>Obese</td>
<td>OR 1.61</td>
<td>Baptiste-Roberts 2012</td>
</tr>
<tr>
<td>GDM</td>
<td>Obese</td>
<td>OR 1.81</td>
<td>Nehring 2013</td>
</tr>
</tbody>
</table>

- Similar findings in rodent experiments.
MATERNAL-NEONATAL DIABETES TRANSMISSION

Adapted from NIH NIDDK 2011
FETAL ORIGINS OF DIABETES

Maternal Diabetes

Offspring Insulin Resistance Later in Life
FETAL ORIGINS OF DIABETES

Maternal Diabetes

- Abnormal Fuel
  - Hyperglycemia
  - Ketone
  - Fatty Acids
  - Amino Acids
- Placental Insufficiency
- Reactive Oxygen Species

Acute Disruption of Fetal Insulin Signaling

Offspring Insulin Resistance Later in Life
FETAL ORIGINS OF DIABETES

Maternal Diabetes

- Abnormal Fuel
  - Hyperglycemia
  - Ketone
  - Fatty Acids
  - Amino Acids
- Placental Insufficiency
- Reactive Oxygen Species

Acute Disruption of Fetal Insulin Signaling

Offspring Insulin Resistance Later in Life
HYPOTHESIS

Fetal exposure to hyperglycemia acutely disrupts fetal insulin signaling and induces insulin resistance later in life
LOCALIZED FETOMATERNAL HYPERGLYCEMIA MODEL

- Catheter placement with tip past the uterine artery take off.

Glucose 4 mg/min
Yao 2010, Gordon 2015

Gestation

48h Glucose infusion

Surgery

Late Effect

Acute Effect
OUTCOME: INSULIN SENSITIVITY

Insulin

Insulin Receptor

AKT

p-AKT
FETAL HYPERGLYCEMIA REDUCES FETAL INSULIN SENSITIVITY

Experimental Timeline

- Surgery
- ±Insulin
- Gestation
- 48h Glucose infusion

Akt Phosphorylation 48 hour after HG Infusion

* N = 23 pups/group, 10 moms, p<0.05
FETAL HYPERGLYCEMIA REDUCES FETAL INSULIN SENSITIVITY

Experimental Timeline

Gestation 48h Glucose infusion

Surgery ± Insulin

Akt Phosphorylation 48 hour after HG Infusion

- N = 23 pups/group, 10 moms, p<0.05
- N = 4 pups/group, 2 mom

Normalized pAkt/Akt Ratio

0.0 0.5 1.0 1.5

Control HG Control HG

Skeletal Muscle Liver

p<0.05
FETAL HYPERGLYCEMIA DECREASES OFFSPRING INSULIN SIGNALING

Experimental Timeline

- **Gestation**
- **Surgery**
- **C section**
- **Cross Foster**
- **Evaluation**

**48 Glucose infusion**

**Postnatal Life**

PND 0

21d

**Soleus Insulin Signaling**

21 day old Offspring

- *p<0.05

- N = 9 vs 19 pups from 6-8 moms

- No difference in liver tissue

- N = 9 vs 19 pups from 6-8 moms

- No difference in liver tissue
FETAL ORIGINS OF DIABETES

Maternal Diabetes

- Abnormal Fuel
  - Hyperglycemia
  - Ketone
  - Fatty Acids
  - Amino Acids
- Placental Insufficiency
- Reactive Oxygen Species

Fetal Hyperglycemia

Fetal Hyperinsulinemia

Acute Disruption of Fetal Insulin Signaling

Offspring Insulin Resistance Later in Life
HYPOTHESIS 2

Fetal hyperinsulinemia during late gestation leads to insulin resistance at postnatal day 21
FETAL HYPERINSULINEMIA MODEL

- Trans-utero injection of long acting insulin (Levemir) vs saline

Nijagal A, 2011
FETAL HYPERINSULINEMIA SUPPRESSED INSULIN SIGNALING ACUTELY

Experimental Timeline

Long acting insulin

Evaluation

Gestation

48 hour

Fetal Akt Phosphorylation 48h after HI

<table>
<thead>
<tr>
<th>pAkt/Akt Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
</tr>
</tbody>
</table>

- Con: Control
- HI: Hyperinsulinemia

Muscle

Liver

Brown Fat

N= 6-8pups/group, 2-3 mother
N= 4 pups/group, 1 mother
N= 4 pups/group, 1 mother

p<0.05
DECREASED LIVER INSULIN STIMULATED AKT-SIGNALING AT PND 21

Experimental Timeline

- **Gestation**
- Long acting insulin
- **48 hour**
- **Natural Birth**
- **21d**

**Evaluation**

---

**Offspring Akt Phosphorylation**

- N=17-18 pups/group, 7 mother
- Con, HI

---

<table>
<thead>
<tr>
<th></th>
<th>Con</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal Muscle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ p<0.05 \]
CONCLUSION

• Fetal hyperglycemia and fetal hyperinsulinemia programs tissue specific insulin resistance
  – Acute/Fetal
    • Hyperglycemia – Insulin resistance in muscle
    • Hyperinsulinemia – Insulin resistance in muscle
  – Postnatal Day 21
    • Hyperglycemia – Insulin resistance in muscle
    • Hyperinsulinemia – Insulin resistance in liver
ACKNOWLEDGEMENT

• Norris Lab
  – Dr Andrew Norris
  – Shanming Hu
  – Dr Jianrong Yao
  – Dr Areej Younes

• University of Iowa
  Division of Neonatology

• Funding
  • FOEDRC
  • CMN grant
  • Marshall Klaus Award
Supplemental Data
STUDY OUTCOME: INSULIN SIGNALING AS MEASURED BY AKT PHOSPHORYLATION
FETAL WEIGHT 48HR AFTER INFUSION

Experimental Timeline

Surgery  Evaluation

Gestation  48h Glucose infusion

Fetal weight 48 after infusion

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.0</td>
</tr>
<tr>
<td>HG</td>
<td></td>
</tr>
</tbody>
</table>

• N = 57 pups/group, 10 moms, *p<0.05
FETAL GLUCOSE AND INSULIN LEVEL

Experimental Timeline

- Surgery
- Evaluation

Gestation 48h Glucose infusion

Fetal Serum Glucose Level

- N = 9 vs 7 pups/group, 4 moms
- P < 0.05

Control

HG

Serum Glucose (mg/dL)

Groups
FETAL GLUCOSE AND INSULIN LEVEL

Experimental Timeline

Gestation

48h Glucose infusion

Experimental Timeline

Surgery

Evaluation

Fetal Serum Glucose Level

Serum Glucose (mg/dL)

Control

HG

Groups

Fetal Insulin Level

Insulin level (ng/ml)

Control

HG

Groups

N = 9 vs 7 pups/group, 4 moms
P < 0.05

N = 9 vs 7 pups/group, 4 moms
FETAL GLUCOSE AND RESPONSE TO INSULIN

Experimental Timeline

- Surgery
- ± Insulin
- Gestation 48h Glucose infusion

Fetal Glucose Level

- N = 13-17 pups/group, 4 moms, P<0.05

Fetal glucose ± Insulin

- N = 2-4 pups/group, 1 mom, linear regression significant

Graphs showing:
- Serum Glucose (mg/dL) for Eu- and Hyperglycemia
- Serum Glucose (mg/dL) for Euglycemia and Hyperglycemia with and without Insulin
FETAL HYPERINSULINEMIA DOES NOT CHANGE FETAL WEIGHT

**Experimental Timeline**
- Gestation
- 48 hour
- Long acting insulin
- Evaluation

**Fetal Weight 48 hour after HI**

- **N=31-35 pups/group, 11 mothers**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Weight (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.00</td>
</tr>
<tr>
<td>HI</td>
<td>1.00</td>
</tr>
</tbody>
</table>
FETAL GLUCOSE LEVEL AND RESPONSE TO EXOGENOUS INSULIN

Experimental Timeline

- Long acting insulin
- Evaluation

Gestation

48 hour

Fetal Serum Glucose 48 hour after HI

Serum Glucose (mg/dL)

Control

HI

Groups

N=10-16 pups/group, 8-10 mothers

Fetal Glucose Level ± Exogenous Insulin

Serum Glucose (mg/dL)

Before

Exogenous Insulin

After

Con

Lev

N=16-21 pups/group, 9-11 mother, slope significant p<0.05