The Role of Maternal Lipids in Fetal Overgrowth: Making Fat from Fat

Oregon Nutrition Update
April 18, 2019

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Objectives

- The Under-recognized role of Lipids in fetal fat accretion
- TG and FFA Results from our research
- How Diet and supplements may lower maternal TGs
- Future Directions

No Disclosures

NIH, ADA
Fetal Programming: Long Term Implications

- Interaction between the genome and epigenome determines a phenotype with susceptibility to chronic disease across the lifespan
  - Friedman JE. Developmental Programming of Obesity and Diabetes, Diab. 2018 Nov;67:2137
  - Barbour, LA Metabolic Culprits in Obesity and GDM; Big Babies, Big Twists, Big Picture, Diab Care, May 2019

- Metabolic factors in the intrauterine environment have a profound effect on prenatal development and enhanced susceptibility to later chronic disease
  - GDM → ↑ fetal Insulin and leptin, fat cell development and number, enlargement of the pancreas, heart, changes in nephron number
  - High fetal insulin/leptin levels affect appetite regulation in the hypothalamus
  - High fat diet in non-human primates → NAFLD, mito function, appetite, behavior
  - Energy expenditure and mitochondrial oxidative capacity affected → obesity and impaired glucose tolerance in childhood; inherit mitochondria from mother
Umbilical Mesenchymal Stem Cells from Offspring form Obese Women Have Greater Adipogenic Potential and Mitochondrial Dysfunction

Can Babies Be Obese?

Updated January 14, 2016 - 7:29 PM ET
Published January 14, 2016 - 3:11 PM ET
Commentary

prove, that children of obese mothers may be more likely — right at the cellular level — to accumulate fat and, thus, at some point, become obese themselves — even if they are not obese as infants. As Time reported:

"Scientists led by a team at University of Colorado School of Medicine analyzed stem cells taken from the umbilical cords of babies born to normal weight and obese mothers. In the lab, they coaxed these stem cells to develop into muscle and fat. The resulting cells from obese mothers had 30 percent more fat than those from normal weight mothers, suggesting that these babies' cells were more likely to accumulate fat."

What are the Earliest Cell Origins of the Fetal Fat Cell??

Human mesenchymal stem cells from offspring of obese mothers have greater adipogenesis and evidence of metabolic dysfunction

Kristen E. Boyle, Zachary W. Patkin, Allison L.B. Shapiro, Dava Dabelea, Jacob E. Friedman

Are babies that don't fall within the "normal" birth weight range at risk of obesity?
Neonatal Fat Mass is Higher in Overweight Pregnant Women

Table 3. Neonatal Body Composition of Infants of Women With Pregavid Body Mass Index (BMI) Less Than 25 Compared With Those With BMI of 25 or More

<table>
<thead>
<tr>
<th></th>
<th>Less Than 25 (n=144)</th>
<th>25 or More (n=76)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3,284±534</td>
<td>3,436±567</td>
<td>.051</td>
</tr>
<tr>
<td>Body composition (TOBEC)</td>
<td>2,951±406</td>
<td>3,023±410</td>
<td>.22</td>
</tr>
<tr>
<td>Lean body mass (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>331±179</td>
<td>406±221</td>
<td>.008</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>9.6±4.3</td>
<td>11±4.7</td>
<td>.006</td>
</tr>
</tbody>
</table>

TOBEC, total body electrical conductivity.
What About NB Fat in Other Places: Like the Liver?
David Brumbaugh MD

• Hepatic fat is associated with NAFLD (40% obese children)

• More rapidly progressive to NASH in kids

• N=13 infants of obese GDM and 12 NW mothers using NMR Spectroscopy

Intrahepatic Fat Is Increased in the Neonatal Offspring of Obese Women with Gestational Diabetes

David E. Brumbaugh, MD,1 Phillip Teare2, Melanie Cree-Green, MD, PhD,1 Laura Z. Fenton, MD,2 Mark Brown, PhD,2 Ann Scherzinger, MD,3 Regina Reynolds, MD,1 Meredith Alston, MD,1 Camille Hoffman, MD,5,6,7, Zhaoxing Pan, PhD,1 Jacob E. Friedman, PhD,1,4, and Linda A. Barbour, MD, MSPH1,4,5

Objectives To assess precision magnetic resonance imaging in the neonate and determine whether there is an early maternal influence on the pattern of neonatal fat deposition in the offspring of mothers with gestational diabetes mellitus (GDM) and obesity compared with the offspring of normal-weight women.

Study design A total of 25 neonates born to normal weight mothers (n = 13) and to obese mothers with GDM (n = 12) underwent magnetic resonance imaging for the measurement of subcutaneous and intra-abdominal fat and magnetic resonance spectroscopy for the measurement of intrahepatic cellular lipid (IHCL) fat at 1–3 weeks of age.

Results Infants born to obese/GDM mothers had a mean 66% increase in IHCL compared with infants born to normal-weight mothers. For all infants, IHCL correlated with maternal prepregnancy body mass index but not with subcutaneous adiposity.

Conclusion Deposition of liver fat in the neonate correlates highly with maternal body mass index. This finding may have implications for understanding the developmental origins of childhood nonalcoholic fatty liver disease. (J Pediatr 2013; 163: ).
• 68% Increase in Hepatic Fat in Neonates Born to Obese GDM mothers

![Graph showing correlation between maternal pre-pregnancy BMI and intrahepatic lipid content.](image)

$r = 0.50, P = 0.02$

• Can Excess Maternal Fat Delivery to the Fetal-Placental Interface Result in the Genesis of NAFLD?
Teasing out Contributors to Excess Fetal Fat Accretion and Childhood Obesity

- 1 in 10 infants and toddlers are obese; 1 in 5 youth *Ogden 2014*

**Factors Associated with high BMI at 2-3 yr:**
- Mat Obesity and Diabetes, Glucose, LGA------Maternal Diet and Lipids
- **Rate of Infant Weight Gain**
  - 0-6 mos infants triple their fat mass; Rapid wt gain birth-2 yrs; Catch up-growth in IUGR
- **Feeding mode** BF protective in most studies; possibly even more so in obesity
Since most macrosomic infants are born to Obese women, could obese women have occult hyperglycemia?

Obese Women have higher Glucoses throughout Day and Night Early and Late in Pregnancy after Fixed Diet

NW vs Obese 1 hr PP: 102 vs 115 mg/dl
NW vs Obese 2 hr PP: 96 vs 107 mg/dl

Body Comp by Skin Calipers only
What About Fat?

Maternal FFAs and TGs found to be better predictors of BW

- Olmos PR, Obesity 2014
- Whyte K, Europ J Ob Gyn 2013
- Misra VK, Obesity 2011
- Vrijkotte TG, Peds 2012
- Hyun Son GA, Acta Obst Gynecol 2010
- Gobl CS, Diab Care 2010
- Schaefer-Graf U, Kjos S, Diab Care 2008
- Akcakus M, 2007
- Di Cianna G, Diabet Med 2005

Normalizing Metabolism in Diabetic Pregnancy: Is It Time to Target Lipids?

Helen L. Barrett,1,2,3 Marloes Dekker Niter,1,3 H. David McIntyre,4 and Leonie K. Calloway,2,3

Diabetes Care 2014;37:1484-1493 | DOI: 10.2337/dc13-1934
Maternal Metabolic Variables Correlating with Infant Body Fat

Harmon, Gerard, Hernandez, Barbour, Bessesen  Diab Care 2011

TG early was strongest correlate of % fat ($r=0.67$);
FFA late ($r=0.54$)

Early Maternal BMI $r=0.55$

BW not correlated with any metabolic variables
Figure 2: Results summary of the association of maternal lipid levels with birthweight throughout pregnancy. The numbers in parenthesis are the number of studies.
What are the independent effects of maternal obesity, maternal body composition, carbohydrate and lipid metabolism on fetal fat accretion and neonatal adiposity?
www.infantgoldresearch.org

(Investigations in Gestational Origins of Lifetime Development)
Major Outcome of Study: Infant DEXA at 2 wks of Age
Birthweight Can Be Deceiving

Mother: Obese & GDM

B.W. = 2893 grams;
body fat = 16.8%

Mother: NW & Normal GT

B.W. = 3370 grams;
body fat 7.7%

Strongest Predictor of childhood adiposity at age 9 yrs is fat mass at birth, not Birth Wt

Catalano  P J Clin Nutr 2009
NIH R01DK078645 “Regulation of Maternal Fuel Supply and Neonatal Adiposity” (2007-16)

Healthy Obese and NL Wt
Eucaloric Diet X3 days;
50% carb; 35% fat; 15% protein; 30% calories

CGMS #1 x 3d
Liquid Breakfast
Mixed Meal Test
10 samples over 4 hrs

Fasting Blood

CGMS #2 x3d
AT Biopsy
Liquid Breakfast
10 samples over 4 hrs
Fetal U/S #1
3-hr OGTT

Fetal U/S #2

Fasting Blood

Delivery
Neonatal Blood/
Anthropometrics
Cord Blood
Placenta

2 weeks PP
Maternal DEXA
Neonatal DEXA/
PeaPod, Anthros

4 mos Pea Pod
Anthros
Diet/Activity Logs

1 yr DEXA Anthros
Blood Draw
Diet/Activity Log
### Maternal and Newborn Characteristics

#### Maternal Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (n=27)</th>
<th>Obese (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.5 ± 0.63</td>
<td>29.8 ± 0.80</td>
</tr>
<tr>
<td>Pre-Pregnancy BMI (kg/m²)</td>
<td>22.3 ± 0.34</td>
<td>31.7 ± 0.62</td>
</tr>
<tr>
<td>Gestational Weight Gain (kg)</td>
<td>13.7 ± 0.84</td>
<td>14.2 ± 1.6</td>
</tr>
<tr>
<td>Primigravida (% total)</td>
<td>14 (51.9)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Caucasian (% total)</td>
<td>25 (92.6)</td>
<td>25 (92.6)</td>
</tr>
</tbody>
</table>

#### Newborn Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight (n=26)</th>
<th>Obese (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age at Delivery</td>
<td>39.7 ± 0.2</td>
<td>39.7 ± 0.23</td>
</tr>
<tr>
<td>Vaginal/Cesarean</td>
<td>20/6</td>
<td>12/7</td>
</tr>
<tr>
<td>Birthweight</td>
<td>3258.0 ± 73.6</td>
<td>3557.6 ± 107.8</td>
</tr>
<tr>
<td>Male/Female</td>
<td>13/13</td>
<td>13/6</td>
</tr>
<tr>
<td>2 Week % Fat</td>
<td>8.9 ± 0.72</td>
<td>11.0 ± 1.2</td>
</tr>
<tr>
<td>2 Week Total Mass</td>
<td>3864.8 ± 95.4</td>
<td>4122.5 ± 136.9</td>
</tr>
</tbody>
</table>

* indicates NW vs. OB p < 0.05

Recruited 60 **HEALTHY** OBESE and NW Women

Dropped: **Del<37 wks**

Obesity Aug 2018
4-Hr AUC Insulin, Gluc, FFA 16 and 28 wks in NW/Obese after Meal

**Insulin** ↑40-50% in OB
--Higher Early in OB than Later in NW

**Glucose** ↑10%

**FFAs** suppressed by high insulin
4 HR AUC TG in NW/Obese after Liquid Meal

OB 30-40% higher early and late

4-Hr AUC-TG completely captured by 1-hr or 2-hr PPTG (r=0.98)
TOT Cohort Mean Early/Late Fasting and PPTG Correlates with %Fat

Mean Fasting TG Early and Late Tot Cohort n = 45

Mean 1 Hr PP TG Early and Late (correlation highest in Boys)

Obesity Aug 2018
NW Moms Increase in Fasting and PP TG from Early to Late Correlates with %Fat

\[ r = 0.59, p < 0.01 \]
\[ r = 0.57, p < 0.01 \]

Delta TG Fasting Early to Late  
\( n = 26 \)

Delta TG AUC Early to Late  
\( n = 26 \)

Obesity Aug 2018
Obese Moms TG **EARLY** Fasting and PP TG Correlates with %Fat

- Fasting TG Early
  - $r=0.60$, $p<0.01$ Early
  - (Late = 0.55)

- 1 Hr PP TG Early
  - $r=0.71$, $p<0.01$ Early
  - (Late = 0.63)

*Obesity Aug 2018*
Develop a Prediction model for Newborn Adiposity:
--Glucose
--Fasting and Postprandial TG (CM-TG and VLDL-TG)
--Differential regulation of AT LPL and Placental (pLPL)
Placenta Seems Important—even for an Endocrinologist

$pLPL$ also hydrolyzes

$\text{TG to FFA} \rightarrow \uparrow \text{FFA}$

for fetal fat accretion?

Margaret Heerwagen PhD, MD

Placental lipoprotein lipase activity is positively associated with newborn adiposity

April 2018
In CHOICE, Maternal TG at GDM Diagnosis Predicts Neonatal Hepatic Fat

Maternal Fasting TG, mg/dL, 32 wks

\[ r = 0.69, \ p = 0.01 \]
\[ n = 13 \]

Maternal 5-hr TG AUC, mg*dL*hr, 32 wks

\[ r = 0.75, \ p = 0.003 \]
\[ n = 13 \]
Can We Intervene with Diet?

Differences in maternal diet peri-conception in Gambian women due to rainy season resulted in changes in maternal plasma key methyl-donors and the methylation of the infant DNA at 2-8 mos in lymphocytes and hair follicles.
Effects of meals rich in either monounsaturated or saturated fat on lipid concentrations and on insulin secretion and action in subjects with high fasting triglyceride concentrations


Sergio Lopez, Beatriz Bermudez, Almudena Ortega, Lourdes M Varela, Yolanda M Pacheco, Jose Villar, Rocio Abia, and Francisco JG Muriana

14 Men with FTG >200; NI OGGT
Cross-over Trial
3 Test Meals Random 1 wk apart
Pasta, slice of brown bread, skim yogurt
Randomized to SFA or MUFA
800 kcal (72% fat; 22% carb; 6% prot)

EITHER:
Olive Oil: Mainly Oleic
  (15% SFA; 81% MUFA; 4% PUFA)
Butter: Mainly Palmitic
  (65% SFA; 31% MUFA; 4% PUFA)

MUFA: Lower TG, FFA, Insulin
-38 OW subjects (age 48; BMI 31) overfed 1,000 extra kcal/day of saturated (SAT) or unsaturated (UNSAT) fat or simple sugars (CARB) for 3 wk -IHTG (1H-MRS); Lipolysis ([2H5]glycerol) and De-Novo Lipogenesis (2H2O) basally and during overfeeding

-SAT ↑Intrahepatic TG (+55%) than UNSAT (+15%, P < 0.05).
-Simple CARB ↑ IHTG (+33%) by stimulating De Novo Lipogenesis (+98%)
-SAT ↑ lipolysis while UNSAT ↓ lipolysis
-SAT induced IR, endotoxemia, and ↑multiple plasma ceramides
# Literature Review for Lowering Post-prandial TG in Pregnancy

## Diet Breakdowns

<table>
<thead>
<tr>
<th>Choice</th>
<th>Conventional</th>
<th><strong>Therapeutic Lifestyle Changes (TLC) (ATP III) 2002</strong></th>
<th>Dietary Approaches to Stop HTN <strong>DASH</strong></th>
<th>Academy of Nutrition and Dietetics <strong>AND/EAL</strong> (2011)</th>
<th>American Heart Association <strong>AHA</strong> (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat</strong></td>
<td>25%</td>
<td>45%</td>
<td>25-35%</td>
<td>27%</td>
<td>25-35%</td>
</tr>
<tr>
<td>SFA</td>
<td>8.75-11.25%</td>
<td>15.75-20.25%</td>
<td>&lt;7%</td>
<td>8%</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>MUFA</td>
<td>8.75-11.25%</td>
<td>15.75-20.25%</td>
<td>Up to 20% of</td>
<td>12%</td>
<td>10-20%</td>
</tr>
<tr>
<td>PUFA</td>
<td>3.75-5%</td>
<td>6.75-9%</td>
<td>Up to 10%</td>
<td>7%</td>
<td>10-20%</td>
</tr>
<tr>
<td>Omega 3</td>
<td>Encouraged +2-4g EPA/DHA Supplement*</td>
<td>EPA/DHA 0.5-1g</td>
<td>EPA/DHA &gt;2g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200mg/day</td>
<td>160mg/d</td>
<td>&lt;200mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHO</strong></td>
<td>60%</td>
<td>40%</td>
<td>50-60%</td>
<td>55%</td>
<td>45-60%</td>
</tr>
<tr>
<td>Simple</td>
<td>70g +/- 5g</td>
<td>70g +/- 5g</td>
<td>158g</td>
<td>Limit added sugar*</td>
<td>&lt;10% added</td>
</tr>
<tr>
<td>Complex</td>
<td>primary source of CHO</td>
<td>primary source of CHO</td>
<td></td>
<td></td>
<td>&lt;100g fructose</td>
</tr>
<tr>
<td>Fiber</td>
<td>20-30g</td>
<td>48g</td>
<td>25-30g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soluble</td>
<td>10-25g</td>
<td>7-13g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>17%</td>
<td>15-20%</td>
</tr>
</tbody>
</table>

*Limit added sugar: <10% of total energy intake from added sugars, <100g fructose.*
TG lowering with 4 g DHA and EPA

Backes, Lipids in Health and Ds 2016, 15:118

**Figure 1.** Higher n-6/n-3 is linked to increased inflammation.

**Table 2.** Change in lipid parameters observed with omega-3 carboxylic acids, omega-3 ethyl esters, and icosapent ethyl in patients with severe hypertriglyceridemia (triglyceride level ≥ 500 mg/dL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OMBCA (Epanova) [17]</th>
<th>OM3EE (Lovaza) [14]</th>
<th>IPE (Vascepa) [16]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (olive oil) (n = 100)</td>
<td>OMBCA 2 g/day (n = 100)</td>
<td>OMBCA 4 g/day (n = 99)</td>
</tr>
<tr>
<td>TG:</td>
<td>Median BL, mg/dL</td>
<td>682</td>
<td>717</td>
</tr>
<tr>
<td></td>
<td>Median percentage change from BL, %</td>
<td>-10</td>
<td>-25</td>
</tr>
</tbody>
</table>
Future Directions

- Validation in larger trial in real world
- Can a Fasting and 2-hr PP TG be used similar to Fasting and 2-hr PP Gluc for Monitoring and Rx for Women at High Risk for Excess Fetal Growth?
- Target Early FTG >125 mg/dl through Diet (↓CM-TG) or Omega 3-FAs in Obese Women (↓VLDL-TG) as possible strategy to ↓ excess Infant Adiposity → Childhood obesity?
- Can this same strategy work for GDM or T2 DM?
Metabolic Culprits In-Utero, Big Babies, Bigger Picture

**MOTHER**
- Genetics
- Epigenetics
- Obesity
- ↑Pre-existing IR
- ↓Beta Cell Reserve
- Metabolic Syndrome
- Diet/Over-Nutrition
- Pregnancy-IR
- Excess Wt Gain
- +/- GDM

**PLACENTA**
- Placental Hormones
- Growth Factors, Sex Nutrient Sensing, Metabolism, Transport
- Glut-1
- FA Transport
- uMSC with ↑ adipogenic potential
- FFA
- Inflammation
- ↑↑ ↑↑

**FETUS**
- ↑↑ Fetal Insulin
- ↑↑ SubQ Fat
- ↑↑ Hepatic Fat
- FA Metabolism
- VLDL-TG
- CM-TG
- EL
- pLPL
- LPS
- Muscle
- Adipose
- Liver
- Gut
- Microbiota
- Mode of Delivery

**NEWBORN**
- Genetics
- Beta Cell Response
- Appetite Reg
- Behavior
- Mito Function
- Stem Cell Diff
- Energy Bal
- Microbiome
- Postnatal
- Over-Feeding
- Rapid Wt Gain
- Microbiome
- Childhood
- Obesity
- NAFLD
- Metabolic Ds
- IR (hPGH, hPL, TNFα, leptin)
- GLUT-1
- AA
- FFA
- AA
- ↑↑
- ↑↑
- ↑
- ↑↑

Barbour, Hernandez 2019
Offspring Health Starts in Utero

Most Macrosomic Infants are Born to Obese Women without GDM or DM

We need to target women at risk by intervening earlier than 16 weeks—
In addition to glucose, also target Pre-Pregnancy BMI and Nutrition, TGs, IR, Postnatal Nutrition
TEAM SCIENCE

Thanks to Moms and Babies!

Teri Hernandez
Jed Friedman
Rachael Van Pelt
Sarah Farabi

Adult and Peds CCTSI; Bionutrition Kitchen; Perinatal Research Team;
NIH R01 DK 078645; NIH R56 DK 078645