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

Oregon Nutrition Update

April 18, 2019

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No Disclosures

NIH, ADA

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

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."

Are babies that don't fall within the "normal" birth weight range at risk of obesity?

SHARE

Neonatal Fat Mass is Higher in Overweight Pregnant Women

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

	Pregravid Body Mass Index		
	Less Than 25 (n=144)	25 or More (n=76)	*P*
Birth weight (g)	3,284±534	3,436±567	.051
Body composition (TOBEC)	2,951±406	3,023±410	.22
Lean body mass (g)			
Fat mass (g)	331±179	406±221	.008
Body fat (%)	9.6±4.3	11±4.7	.006

TOBEC, total body electrical conductivity.

Catalano PM 2007;109:419

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

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

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

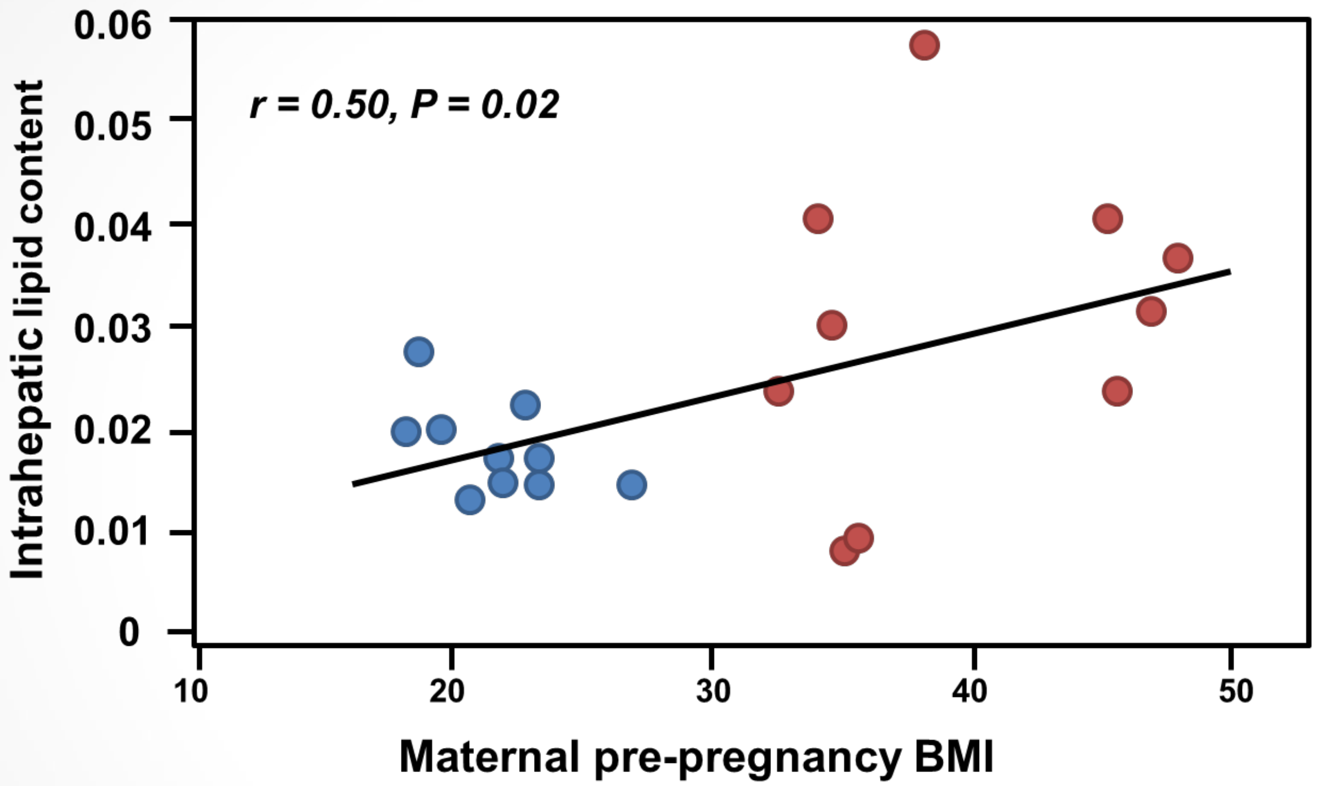
Objectives To assess precision magnetic resonance imaging in the neonate and determine whether there is an early maternal influence on the pattern of neonatal fat deposition in the offspring of mothers with gestational diabetes mellitus (GDM) and obesity compared with the offspring of normal-weight women.
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 intrahepatocellular lipid (IHCL) fat at 1-3 weeks of age.
Results Infants born to obese/GDM mothers had a mean 68% 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;■:■-■).*

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

- **68% Increase in Hepatic Fat in Neonates Born to Obese GDM mothers**



- ***Can Excess Maternal Fat Delivery to the Fetal-Placental Interface Result in the Genesis of NAFLD?***

Brumbaugh, 2013.

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

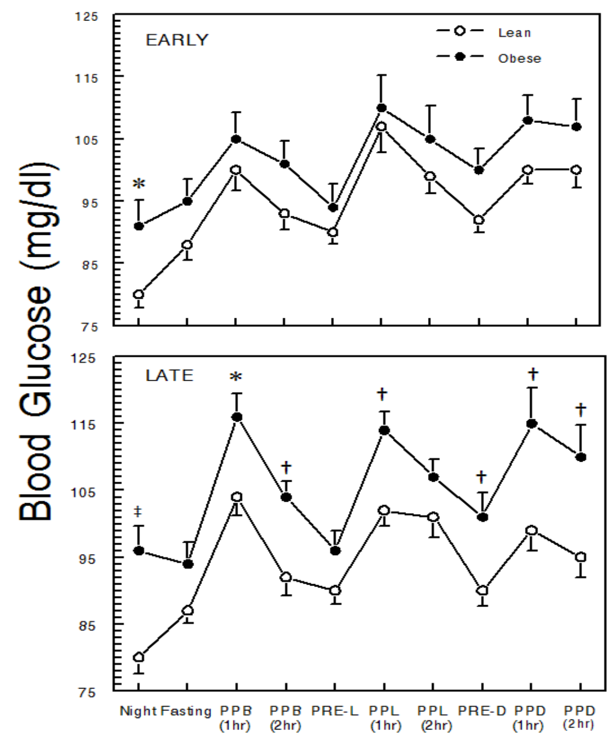
Since most macrosomic infants are born to Obese women, could obese women have occult hyperglycemia?

Continuous Glucose Profiles in Obese and Normal-Weight Pregnant Women on a Controlled Diet Diabetes Care 2011 34:2198

Metabolic determinants of fetal growth

KRISTIN A. HARMON, MD[1]
LORI GERARD, MD[1]
DALAN R. JENSEN, MS[1]
ELIZABETH H. KEALEY, BS[2]
TERI L. HERNANDEZ, PHD, RN[1,3]
MELANIE S. REECE, PHD[4]
LINDA A. BARBOUR, MD, MSPH[1,5]
DANIEL H. BESSESEN, MD[1]

macrosomia (birth weight >4,000 g) than does gestational diabetes (3). Although the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial demonstrated that



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 Lipids and Fetal Overgrowth: Making Fat from Fat

Clin Ther 2018

Linda A. Barbour, MD, MSPH[1,2] and Teri L. Hernandez, PhD, RN[1,3]

Maternal lipid levels during pregnancy and child weight status at 3 years of age

Pediatric Obesity. 2018;e12485.

Chantel L. Martin[1] | Catherine J. Vladutiu[2,3] | Tarek M. Zikry[4] | Matthew R. Grace[5] | Anna Maria Siega-Riz[6]

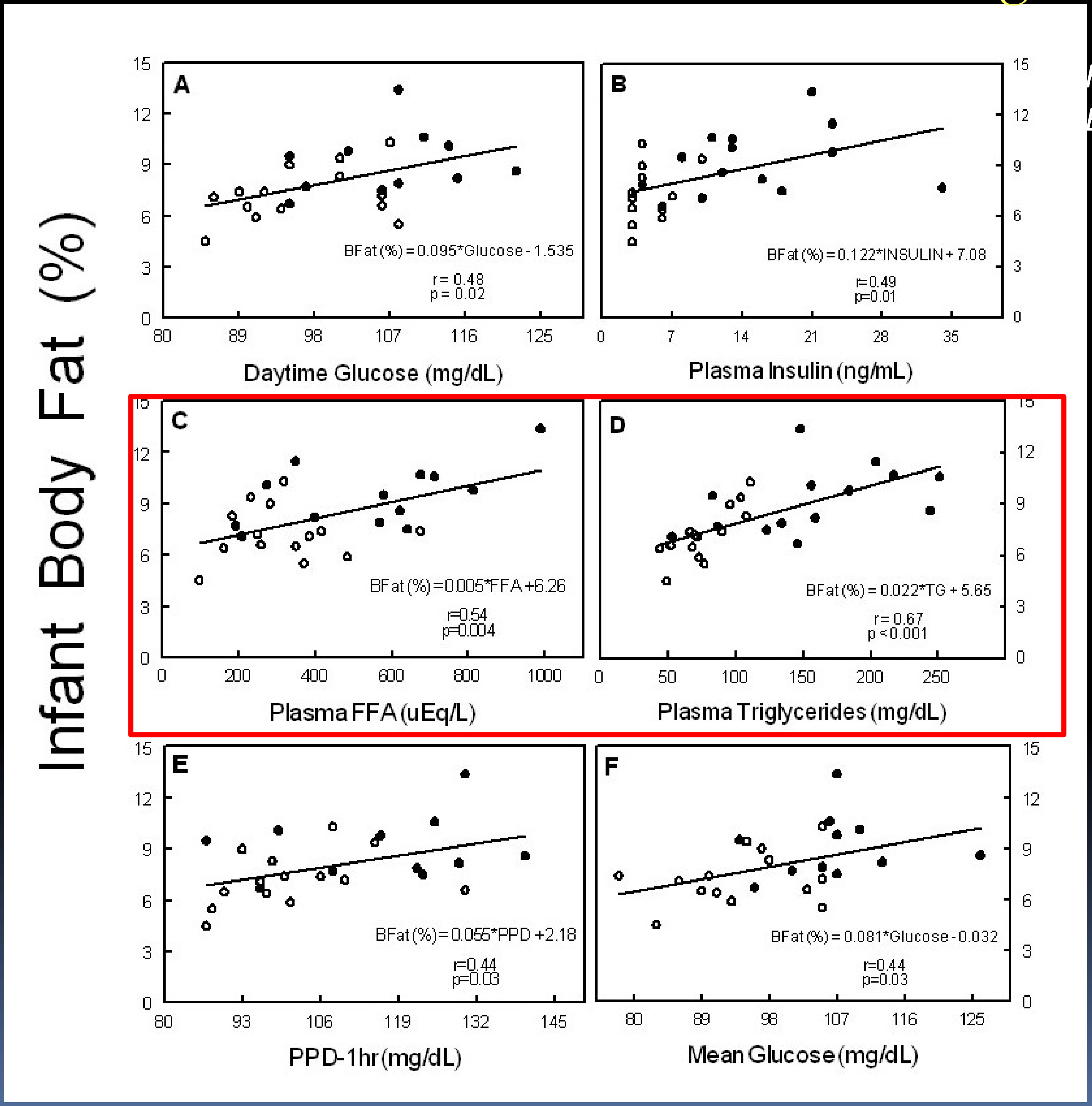
- Maternal FFAs and TGs found to be better predictors of BW
  - Olmos PR *Obesity 2014*
  - Whyte K *Europ J Ob Gyn 2013*
  - Misra VK *Obesity 2011*
  - Vrijkotte TG *J Peds* 2012
  - Hyun Son GA *Acta Obst Gynecol 2010*
  - Gobl CS *Diab Care 2010*
  - Schaefer-Graf U, Kjos S *Diab Care 2008*
  - Akcakus 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 Nitert,[1,3] H. David McIntyre,[3,4] and Leonie K. Callaway[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

Gestational dyslipidaemia and adverse birthweight outcomes: a systematic review and meta-analysis

Obesity Reviews 2018

J. Wang[1,2], D. Moore[2], A. Subramanian[2], K. K. Cheng[2], K. A. Toulis[2], X. Qiu[1], P. Saravanan[3], M. J. Price[2] and K. Nirantharakumar[2]

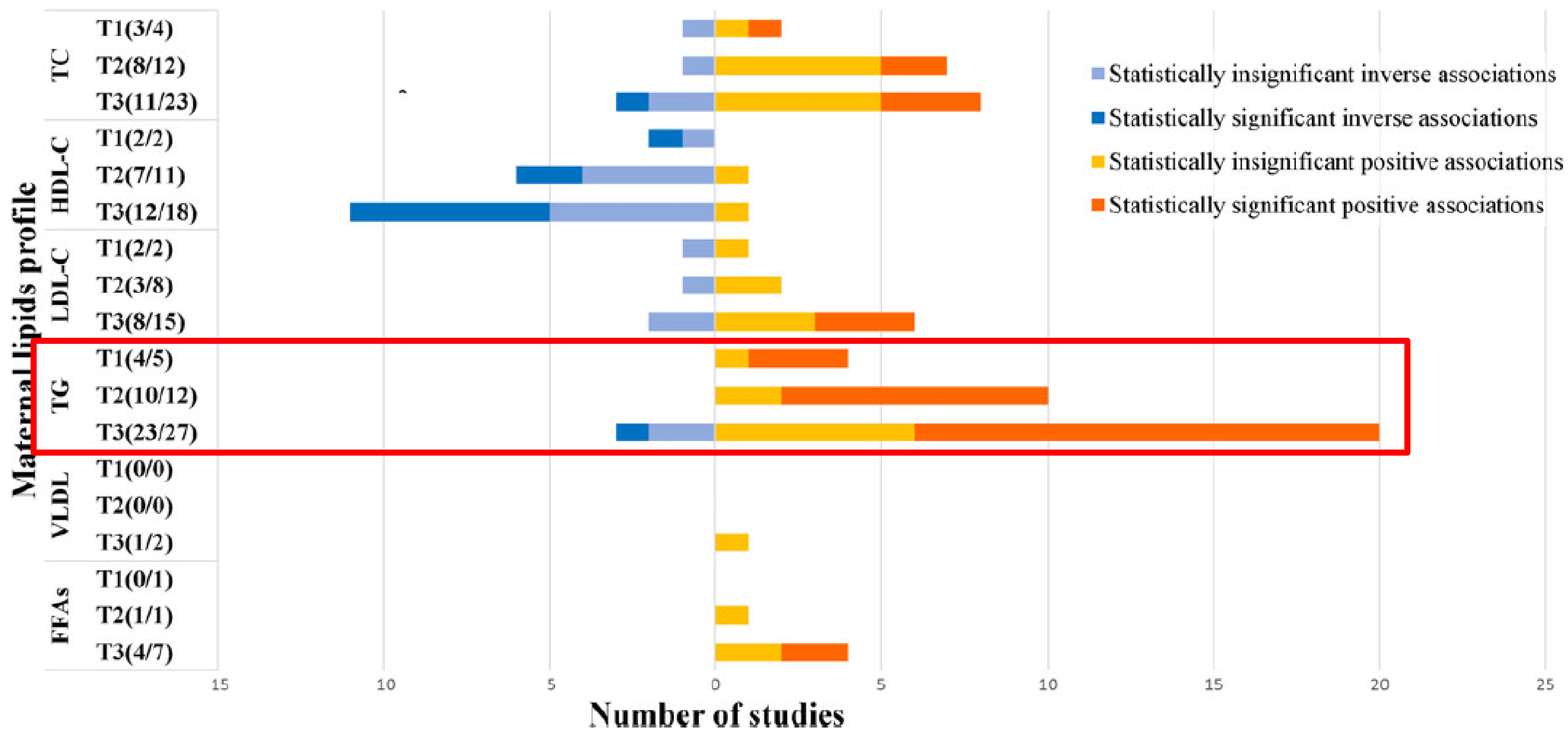
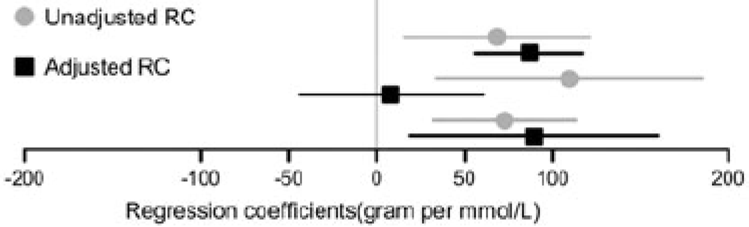


Figure 2 Results summary of the association of maternal lipid levels with birthweight throughout pregnancy. The numbers in parenthesis are the number

TG				
The 1st trimester	2052/4666	1/5	NA	86.72(45.14, 117.30)
The 2nd trimester	804/6009	1/12	NA	7.97(-44.18, 60.12)
The 3rd trimester	4118/11363	8/27	93%	89.58(18.52, 160.25)

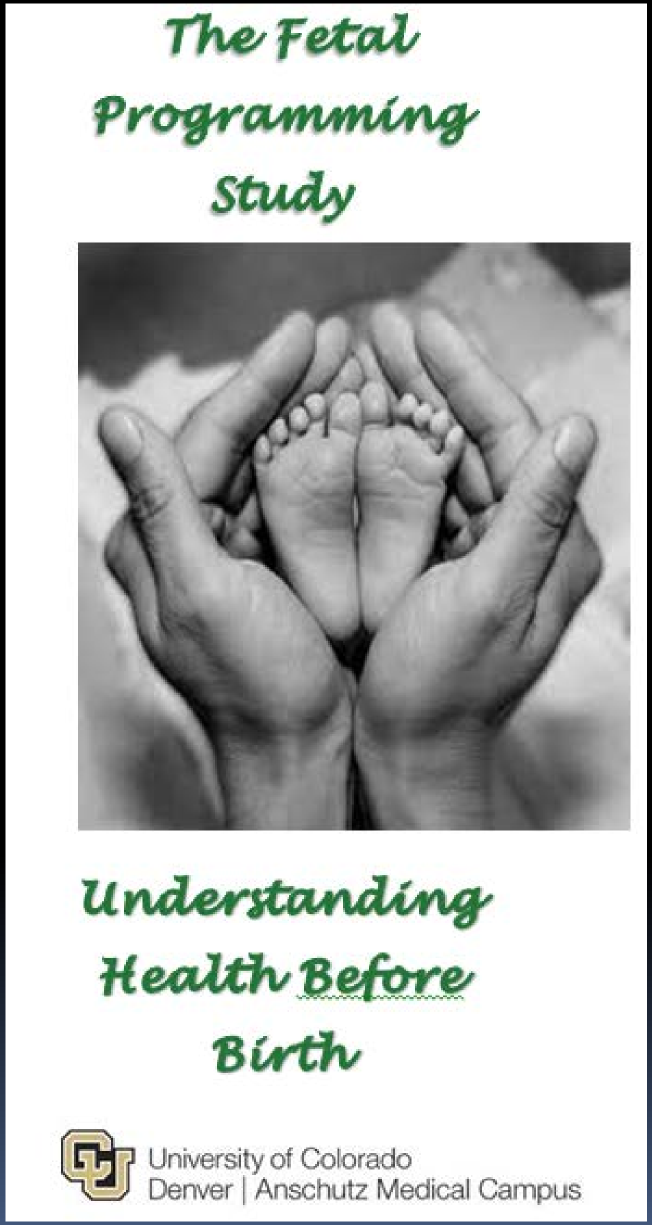


Regulation of Maternal Fuel Supply and Neonatal Adiposity

NIH R56→2007-2009

R01DK078645 2010-2015

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

(**I**nvestigations in **G**estational **O**rigins of **L**ifetime **D**evelopment)

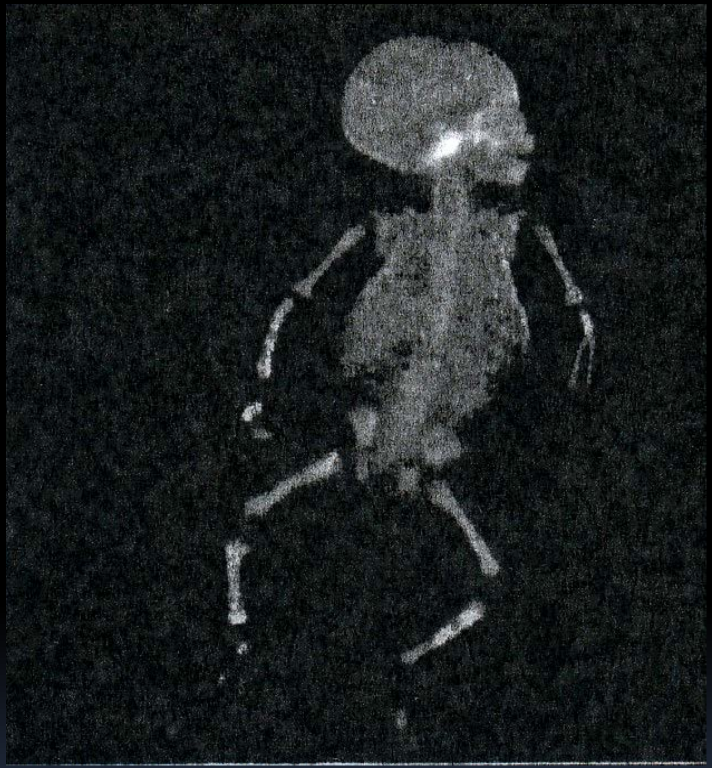
Nicole Hirsch
Sarah Farabi
Libby Haugen
Emily Zans
Kristy Heiss

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

Fasting Blood
Fetal U/S #2

12 13 **14** **15** 16 17 18 19 20 21 22 23 **24** 25 **26** **27** **28** 29 30 31 32 33 34 35 **36** 37 38 39 **40**

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		
	Normal Weight (n=27)	Obese (n=27)
Age (years)	30.5 ± 0.63	29.8 ± 0.80
Pre-Pregnancy BMI (kg/m^2)	22.3 ± 0.34	31.7 ± 0.62
Gestational Weight Gain (kg)	13.7 ± 0.84	14.2 ± 1.6
Primigravida (% total)	14 (51.9)	11 (40.7)
Caucasian (% total)	25 (92.6)	25 (92.6)

Newborn Characteristics		
	Normal Weight (n=26)	Obese (n=19)
Gestational Age at Delivery	39.7 ± 0.2	39.7 ± 0.23
Vaginal/Cesarean	20/6	12\7
Birthweight	3258.0 ± 73.6	3557.6 ± 107.8 +
Male/Female	13/13	13/6
2 Week % Fat	8.9 ± 0.72	11.0 ± 1.2
2 Week Total Mass	3864.8 ± 95.4	4122.5 ± 136.9

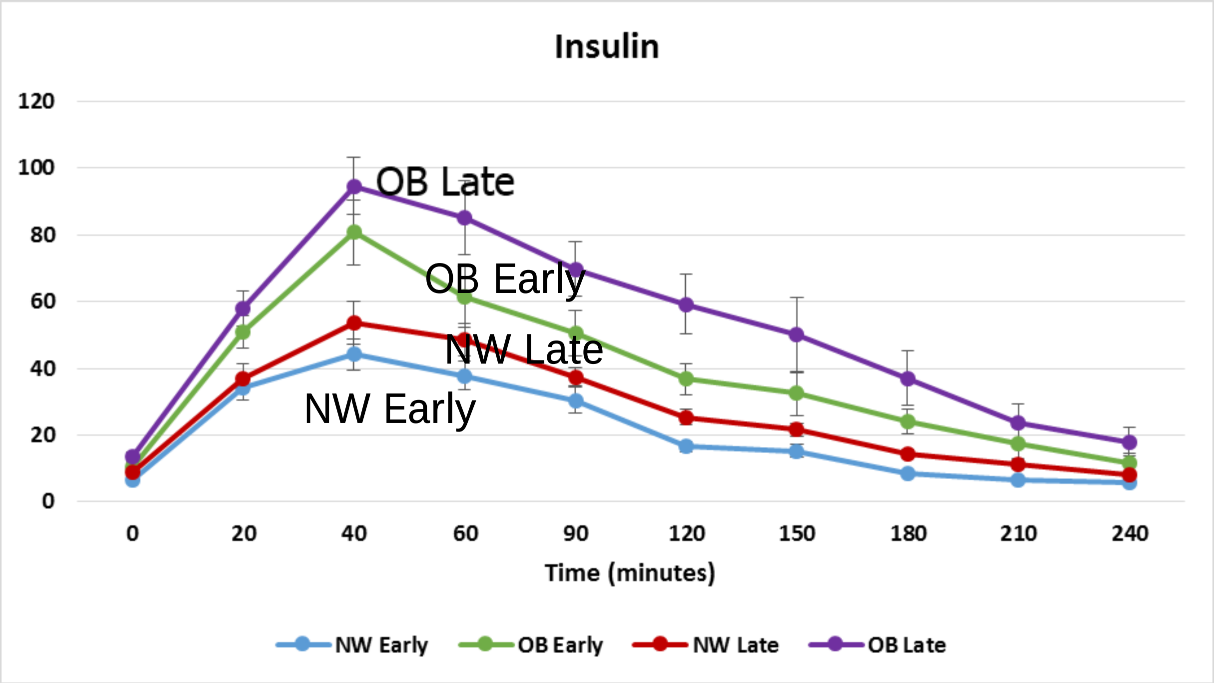
+ indicates NW vs. OB $p < 0.05$

Recruited 60 **HEALTHY** OBESE and NW Women

Dropped: **Del<37 wks**

Obesity Aug 2018

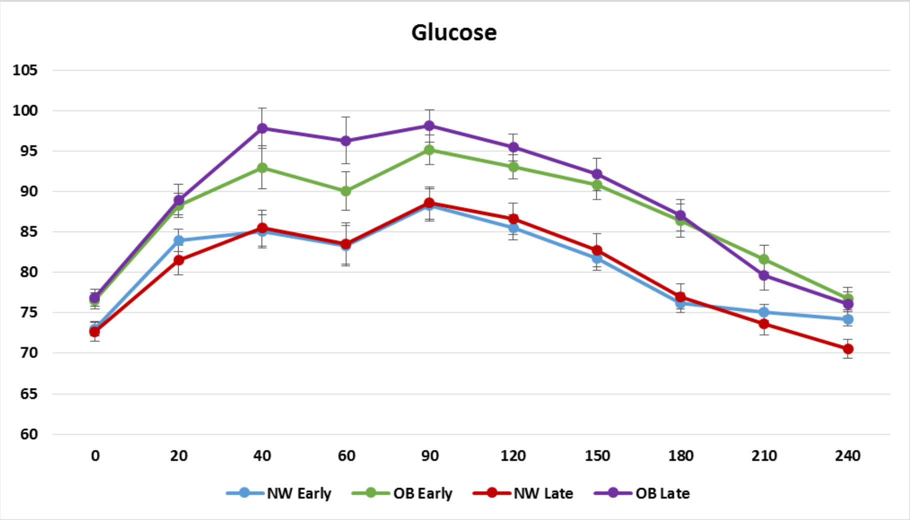
4-Hr AUC Insulin, Gluc, FFA 16 and 28 wks in NW/Obese after Meal

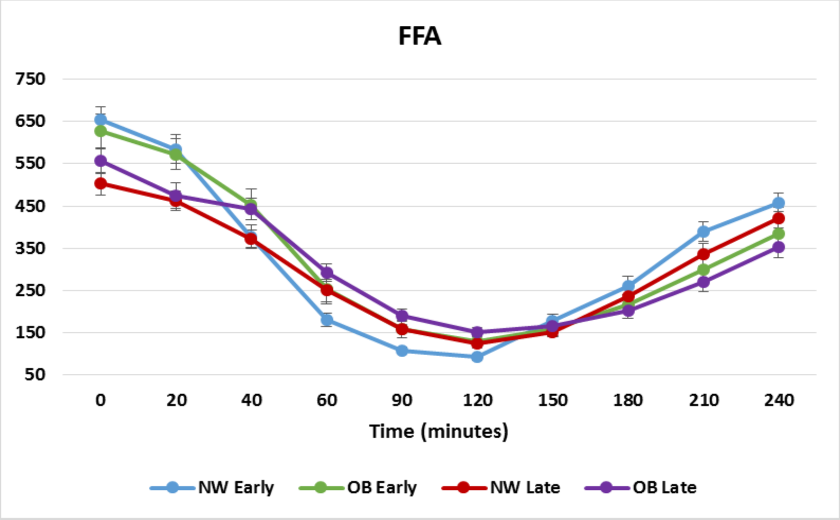


Insulin ↑40-50 % in OB
--Higher Early in OB than Later in NW

Glucose ↑10%

FFAs suppressed by high insulin



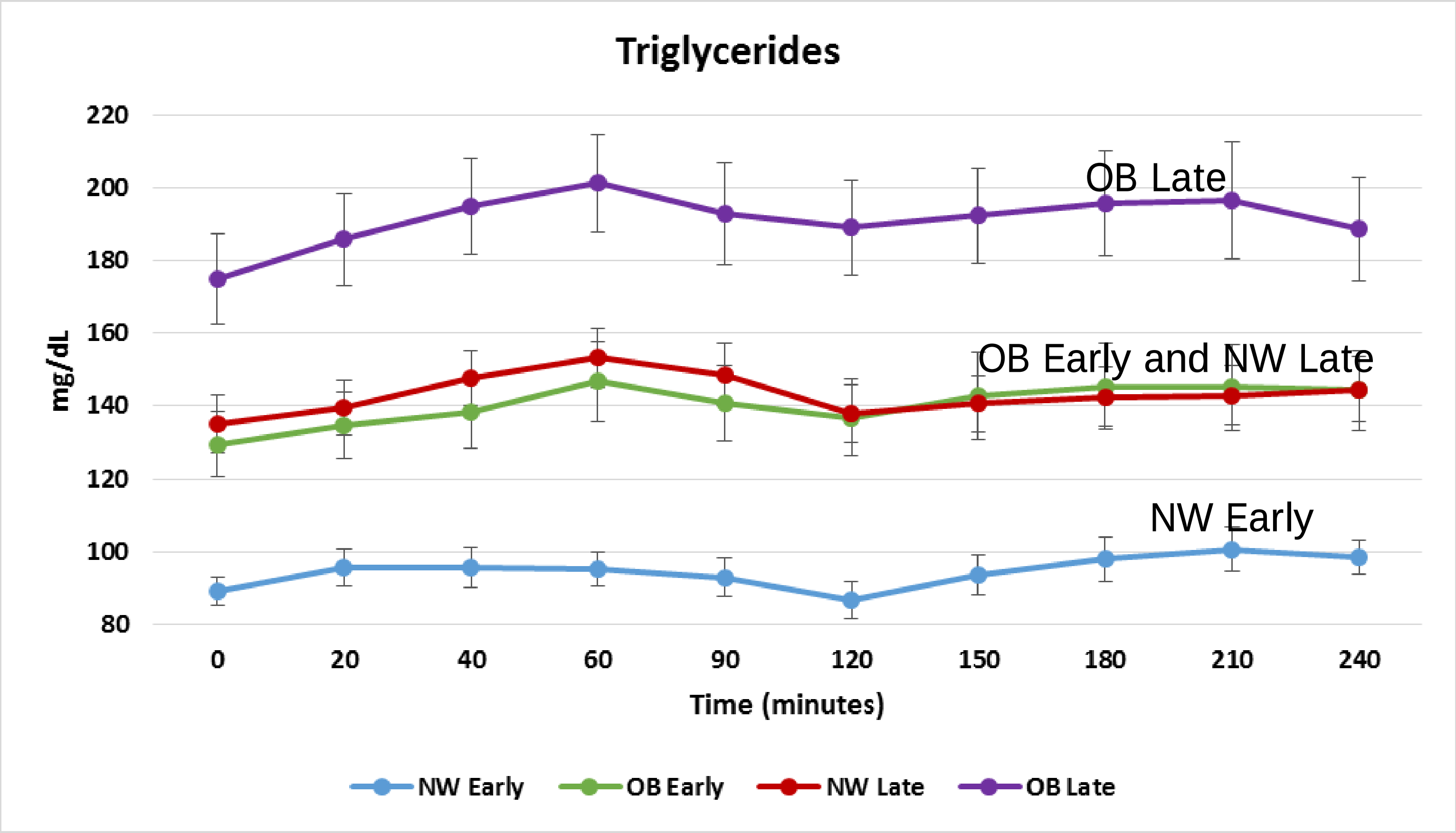


Postprandial Triglycerides Predict Newborn Fat More Strongly than Glucose in Women with Obesity in Early Pregnancy

Obesity 2018

Linda A. Barbour[1,2], Sarah S. Farabi[1], Jacob E. Friedman[1,3], Nicole M. Hirsch[1], Melanie S. Reece[1], Rachael E. Van Pelt[4*], and Teri L. Hernandez[1,5*]

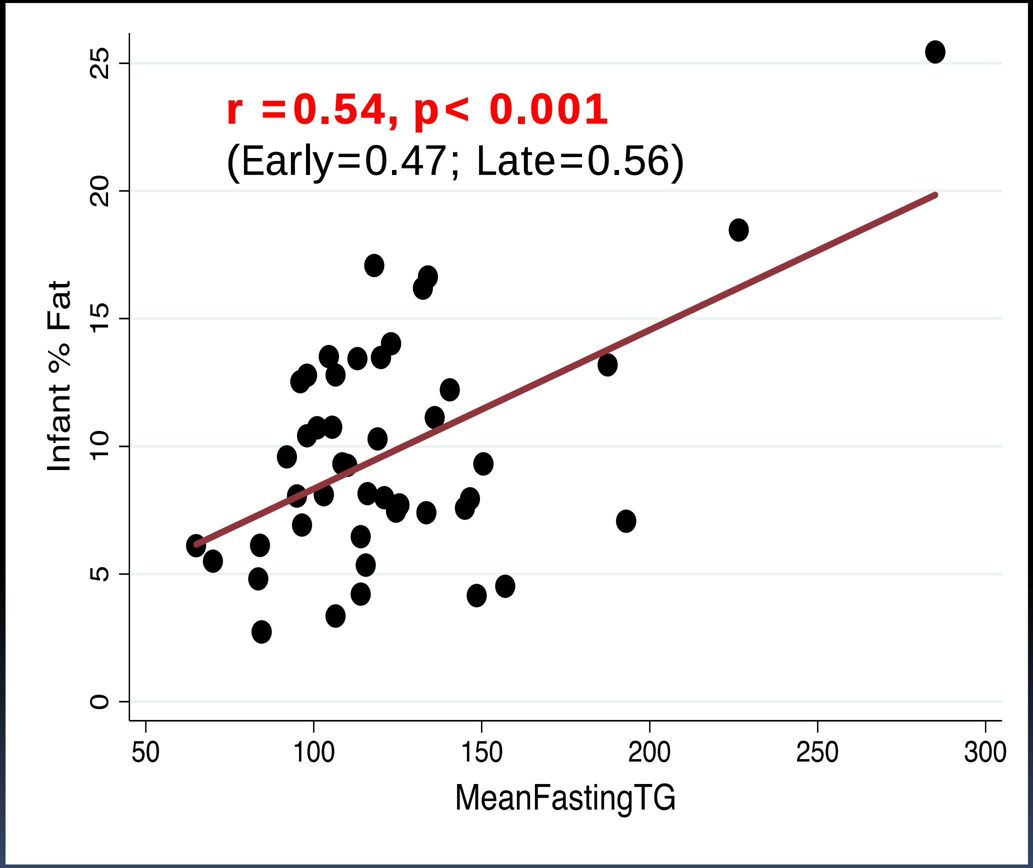
4 HR AUC TG in NW/Obese after Liquid Meal



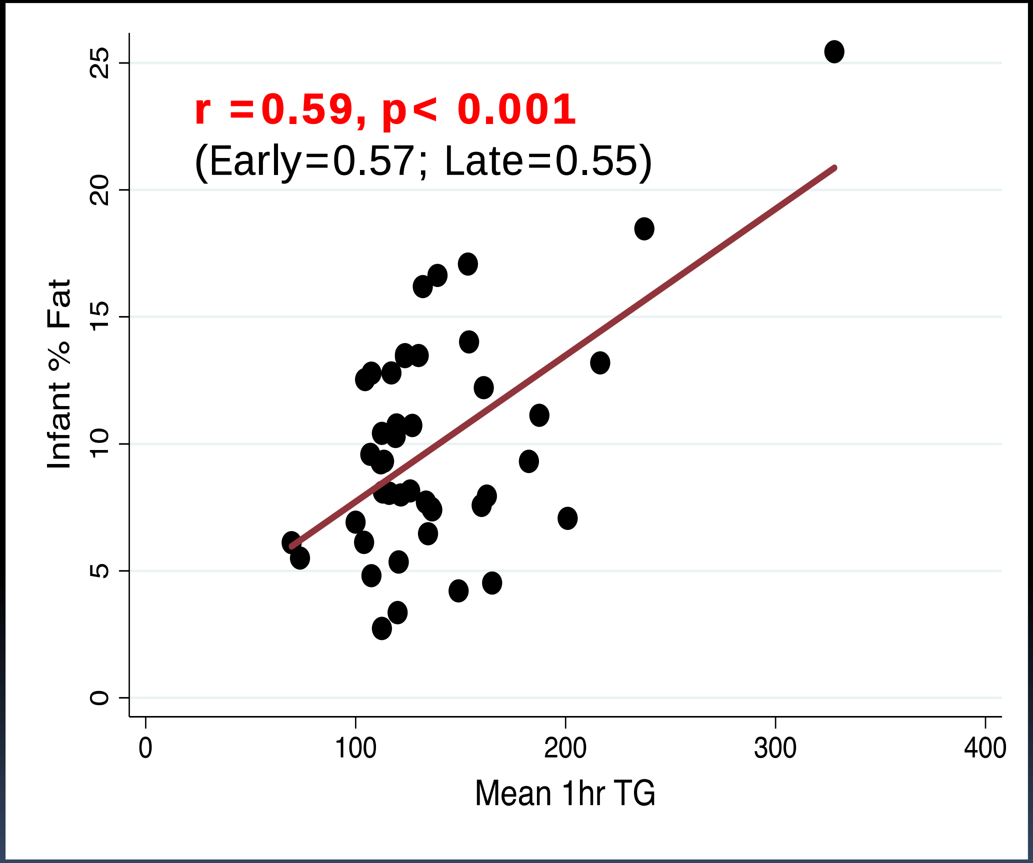
OB 30-40% higher early and late

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



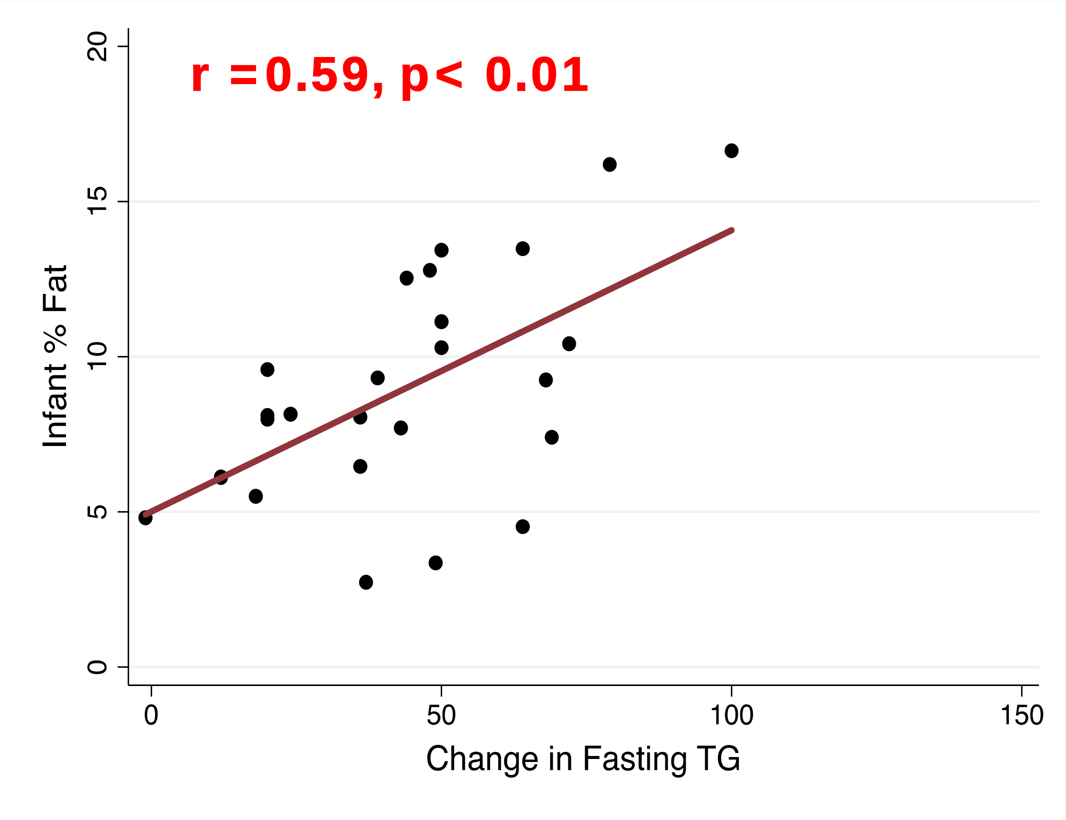
Mean Fasting TG Early and Late
Tot Cohort n = 45

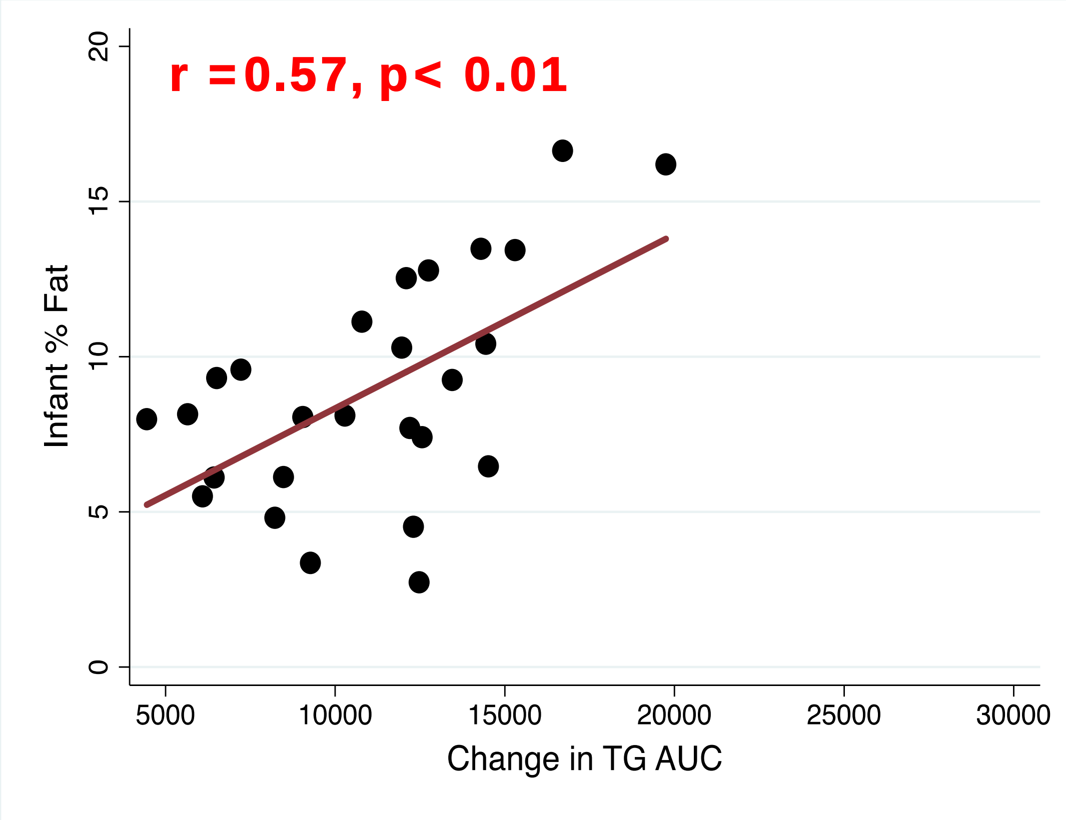


Mean 1 Hr PP TG Early and Late
(correlation highest in Boys)

Obesity Aug 2018

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



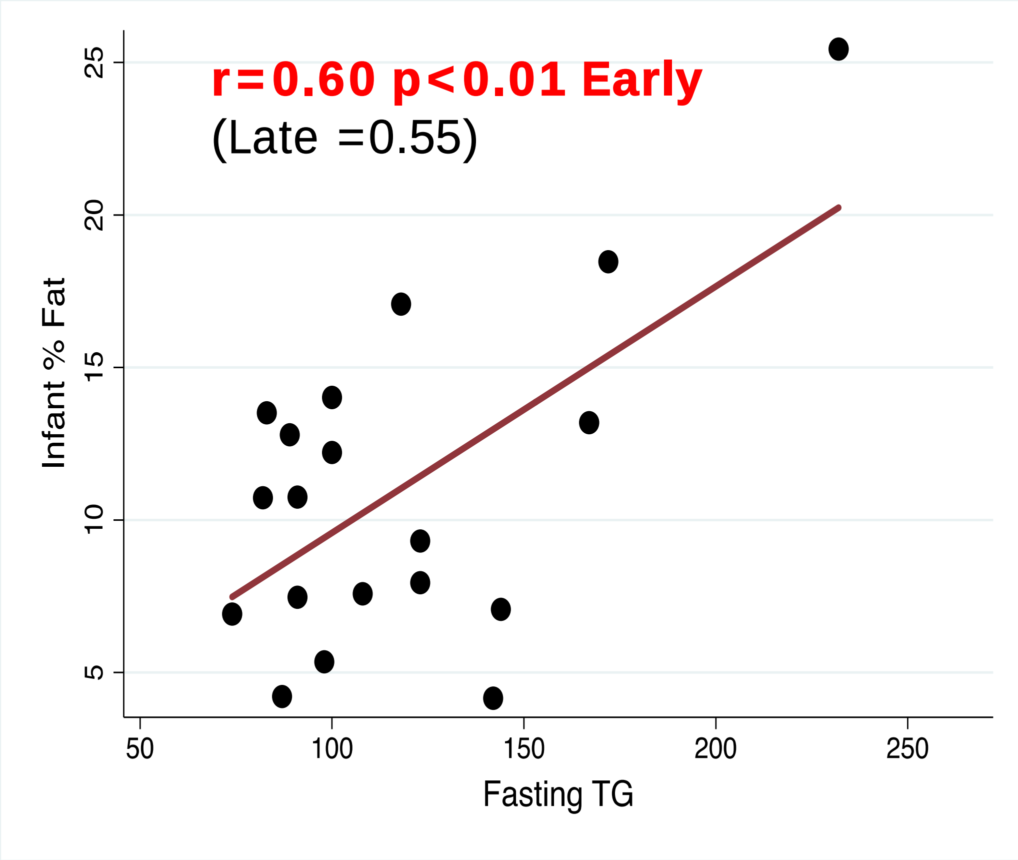


Delta TG Fasting Early to Late
n = 26

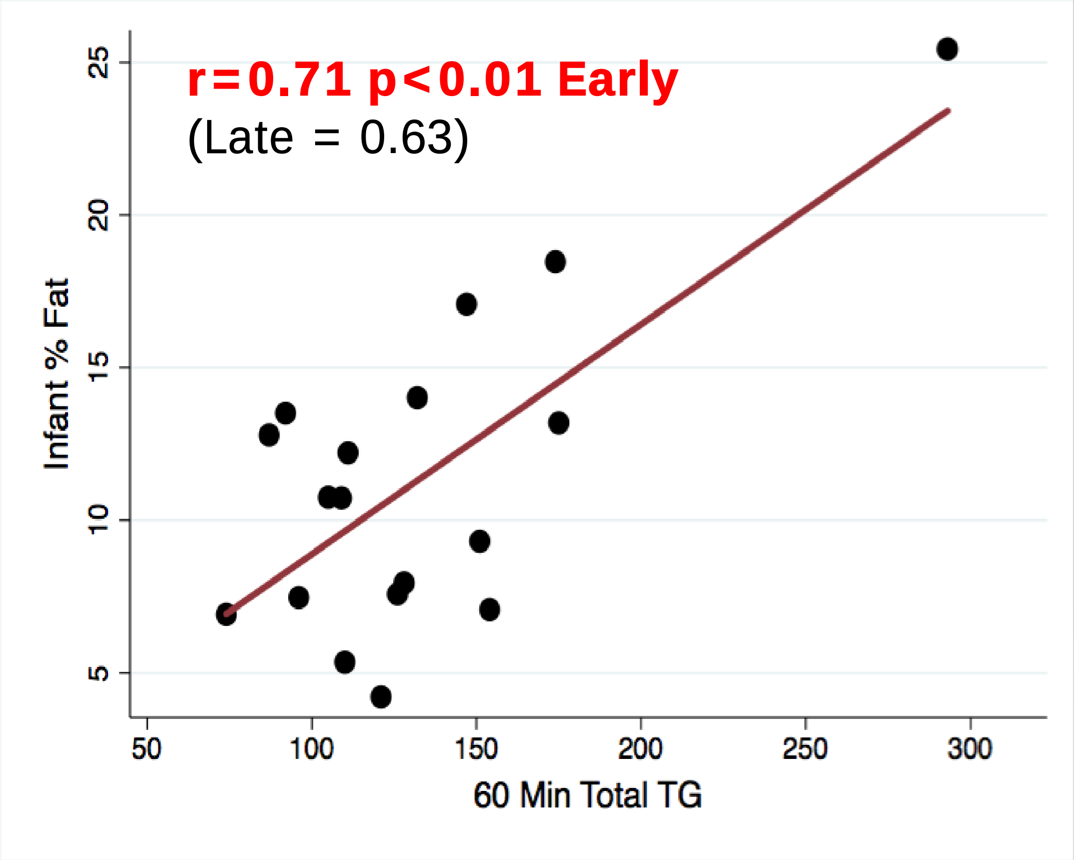
Delta TG AUC Early to Late
n = 26

Obesity Aug 2018

Obese Moms TG EARLY Fasting and PP TG Correlates with %Fat



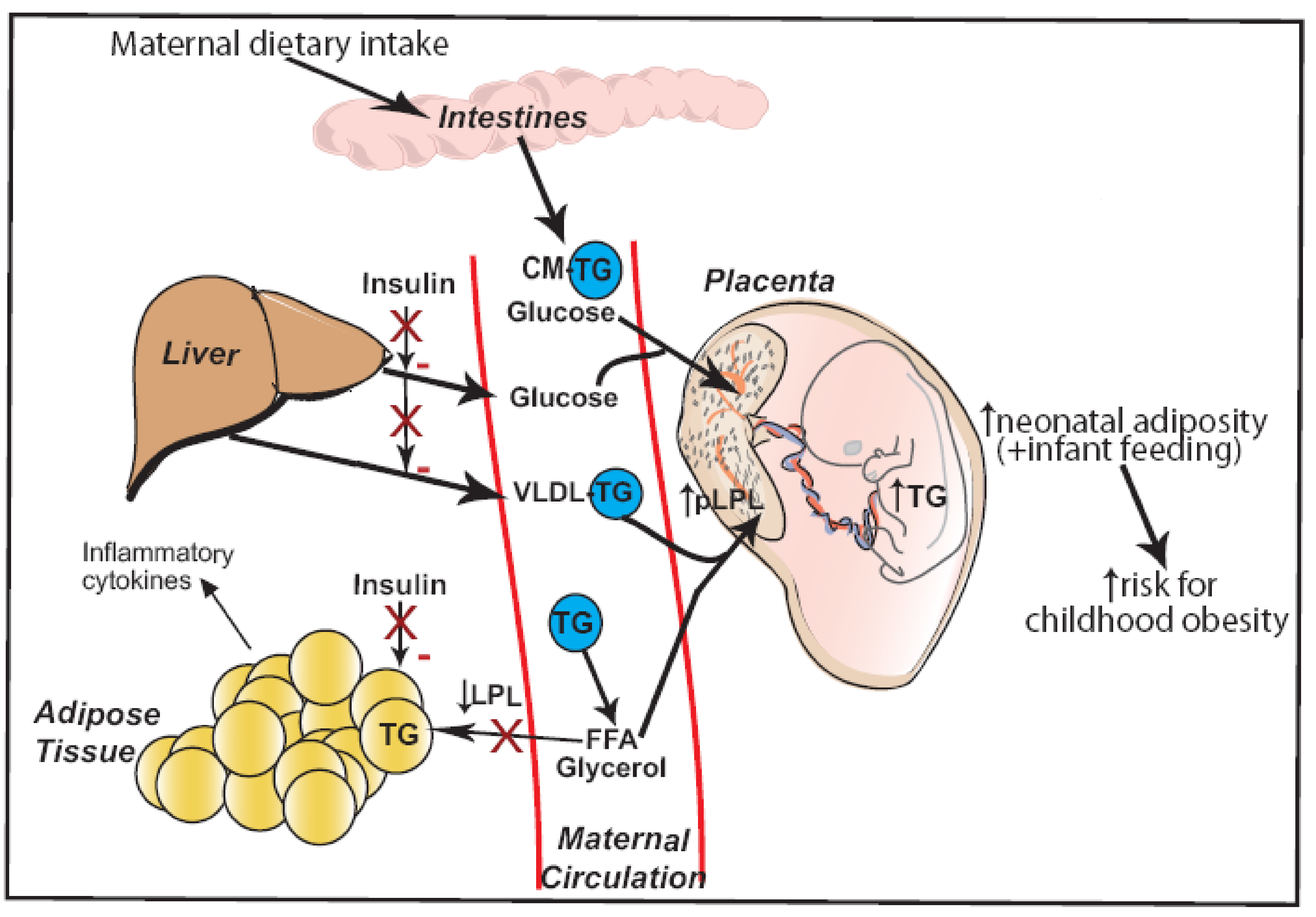
Fasting TG Early
n=19



1 Hr PP TG Early

Obesity Aug 2018

R01 DK078645 Regulation of Maternal Fuel Supply and Infant Fat Mass



Develop a Prediction model for Newborn Adiposity:

--Glucose

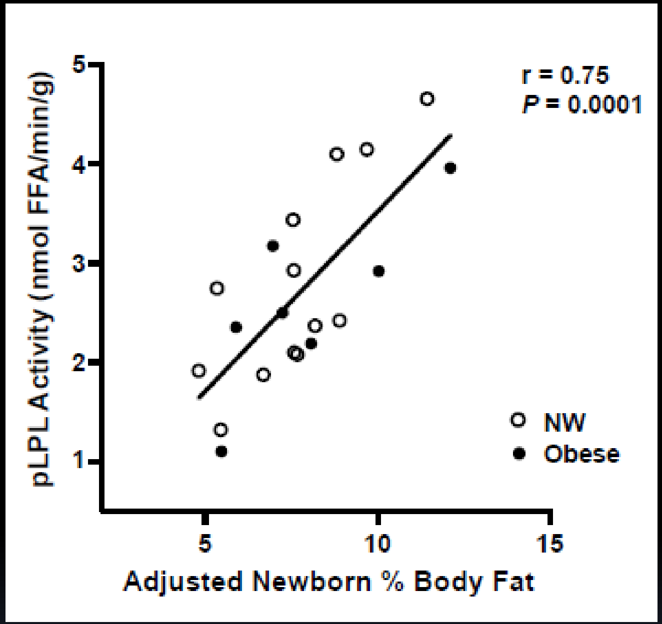
--Fasting and Postprandial TG (CM-TG and VLDL-TG)

--Differential regulation of AT LPL and Placental (pLPL)

Placenta Seems Important—even for an Endocrinologist

Margaret Heerwagen PhD, MD

pLPL also hydrolyzes TG to FFA→↑FFA for fetal fat accretion?



Contents lists available at ScienceDirect

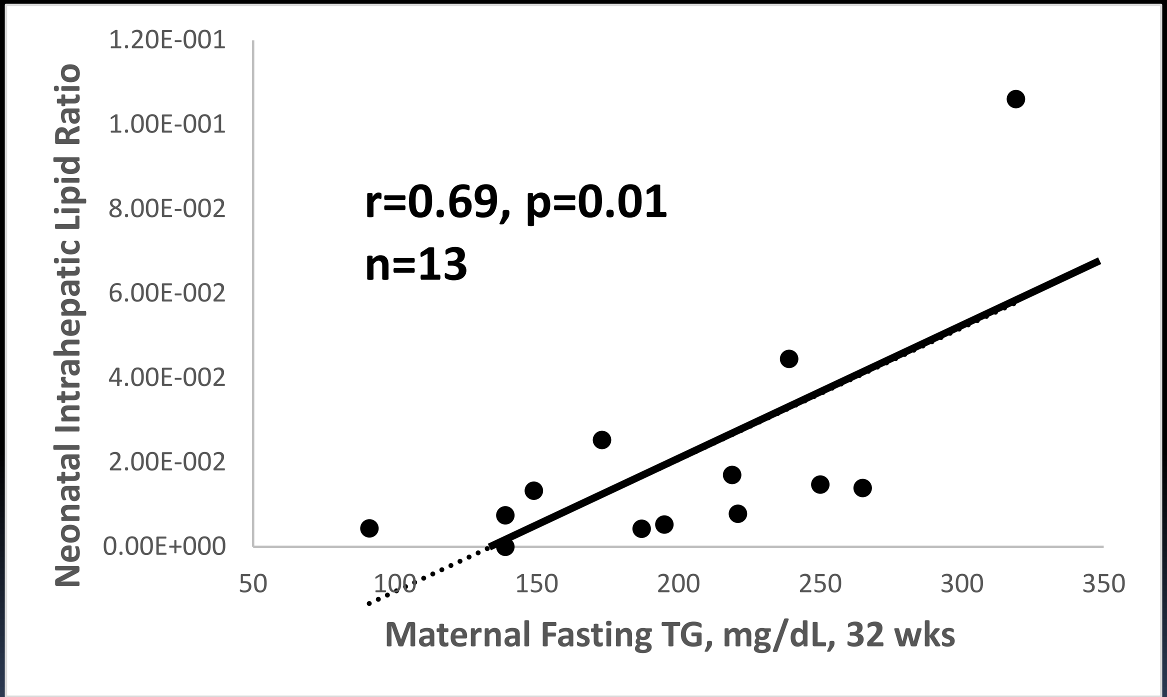
Placenta April 2018

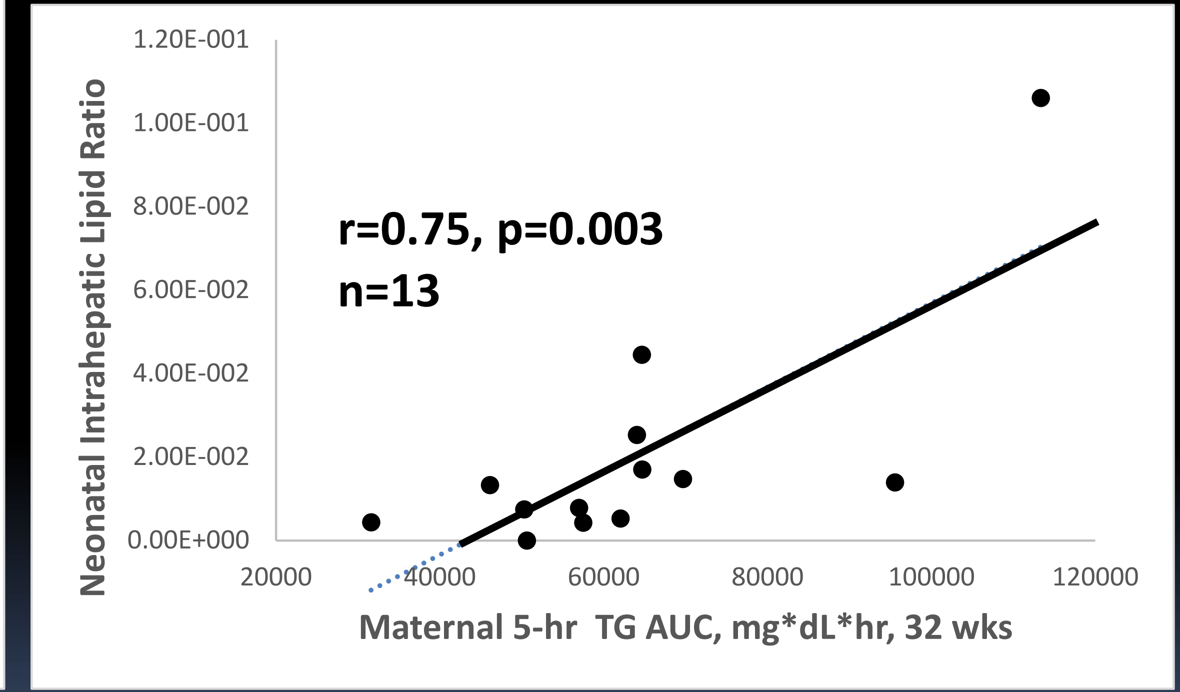
journal homepage: www.elsevier.com

Placental lipoprotein lipase activity is positively associated with newborn adiposity

Margaret J.R. Heerwagen[a, b, 1], Diane L. Gumina[a], Teri L. Hernandez[c, d], Rachael E. Van Pelt[e], Anita W. Kramer[a], Rachel C. Janssen[b], Dalan R. Jensen[c], Theresa L. Powell[a, b], Jacob E. Friedman[b, c, f], Virginia D. Winn[a, 2], Linda A. Barbour[a, c, *]

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





Can We Intervene with Diet?

Babies of women who eat junk food while pregnant 'more likely to be obese'

Babies of women who eat junk food while pregnant will be more likely to be obese as an adult and will be born with an addiction to fatty foods, Australian scientists have concluded.

Babies of women who eat junk food while pregnant will be born with an addiction to fatty foods Photo: PA

Diet Composition at Conception Can Influence Child's Epigenome

Differences in mat 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

nature COMMUNICATIONS

ARTICLE

Received 27 Nov 2013 | Accepted 26 Mar 2014 | Published 29 Apr 2014 DOI: 10.1038/ncomms4746 OPEN

Maternal nutrition at conception modulates DNA methylation of human metastable epialleles

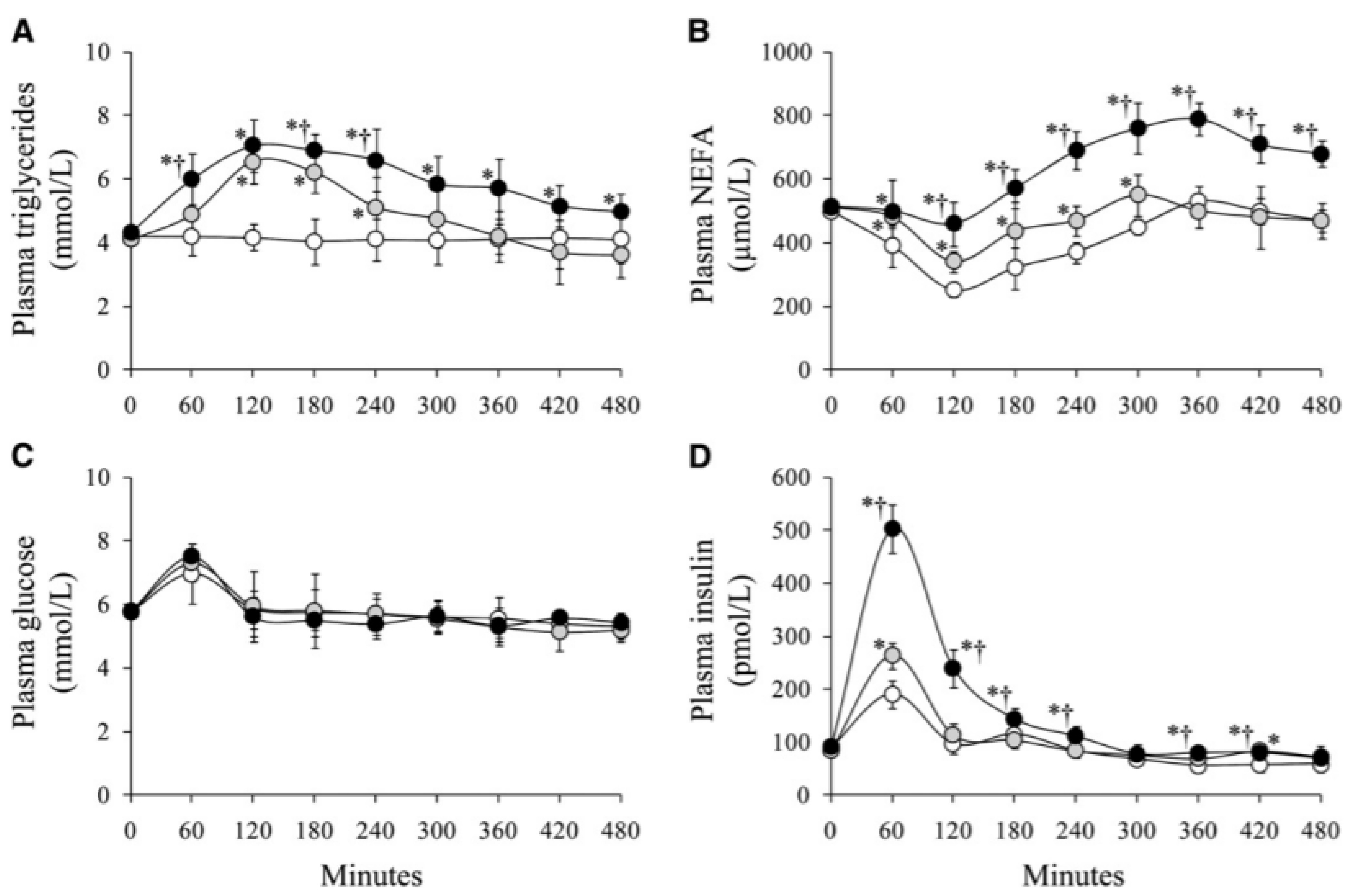
Paula Dominguez-Salas[1], Sophie E. Moore[1], Maria S. Baker[2], Andrew W. Bergen[3], Sharon E. Cox[1], Roger A. Dyer[4], Anthony J. Fulford[1], Yongtao Guan[2,5], Eleonora Laritsky[2], Matt J. Silver[1], Gary E. Swan[6], Steven H. Zeisel[7], Sheila M. Innis[4], Robert A. Waterland[2,5], Andrew M. Prentice[1] & Branwen J. Hennig[1]

In experimental animals, maternal diet during the periconceptional period influences the establishment of DNA methylation at metastable epialleles in the offspring, with permanent phenotypic consequences. Pronounced naturally occurring seasonal differences in the diet of rural Gambian women allowed us to test this in humans. We show that significant seasonal variations in methyl-donor nutrient intake of mothers around the time of conception influence 13 relevant plasma biomarkers. The level of several of these maternal biomarkers predicts increased/decreased methylation at metastable epialleles in DNA extracted from lympho-cytes and hair follicles in infants postnatally. Our results demonstrate that maternal nutri-tional status during early pregnancy causes persistent and systemic epigenetic changes at human metastable epialleles.

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[1–4]

Am J Clin Nutr 2011;93:494–9.

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; Nl OGTT
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

Saturated Fat Is More Metabolically Harmful for the Human Liver Than Unsaturated Fat or Simple Sugars

Panu K. Luukkonen
Diab Care 2018

-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

	CHOICE	Conventional	Therapeutic Lifestyle Changes (TLC) (ATP III) 2002	Dietary Approaches to Stop HTN DASH	Academy of Nutrition and Dietetics AND/EAL (2011)	American Heart Association AHA (2011)	
						Fasting TG 150-199	Fasting TG >500
Fat	**25%**	**45%**	**25-35%**	**27%**	**25-35%**	**25-35%**	**20-35%**
SFA	8.75-11.25%	15.75-20.25%	<7%	8%	<7%	<7%	<5%
MUFA	8.75-11.25%	15.75-20.25%	Up to 20% of	12%		10-20%	10-20%
PUFA	3.75-5%	6.75-9%	Up to 10%	7%		10-20%	10-20%
Omega 3					Encouraged +2-4g EPA/DHA Supplement*	EPA/DHA 0.5-1g	EPA/DHA >2g
Cholesterol			<200mg/day	160mg/d	<200mg		
CHO	**60%**	**40%**	**50-60%**	**55%**	**45-60%**	**50-60%**	**45-50%**
Simple	70g +/- 5g	70g +/- 5g		158g	Limit added sugar*	<10% added <100g fructose	<5% added <50g fructose
Complex			primary source of CHO		primary source of CHO		
Fiber			20-30g	48g	25-30g		
Soluble			10-25g		7-13g		
Protein	**15%**	**15%**	**15%**	**17%**	**15-20%**	**15%**	**20%**

TG lowering with 4 g DHA and EPA

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

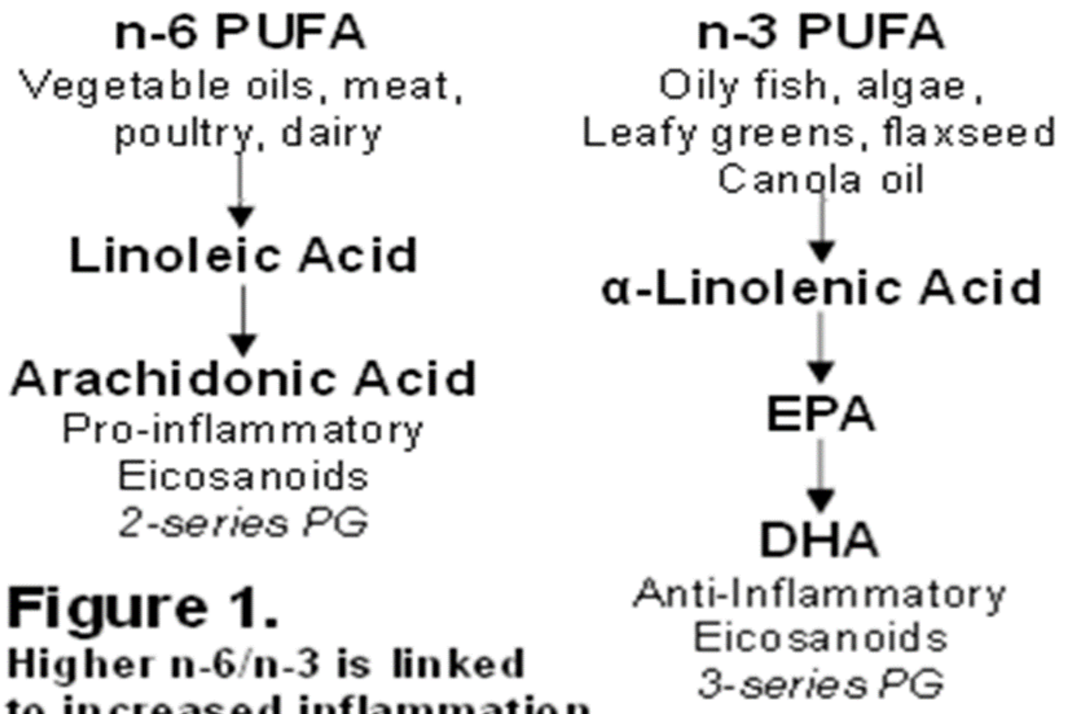


Figure 1. **Higher n-6/n-3 is linked to increased inflammation.**

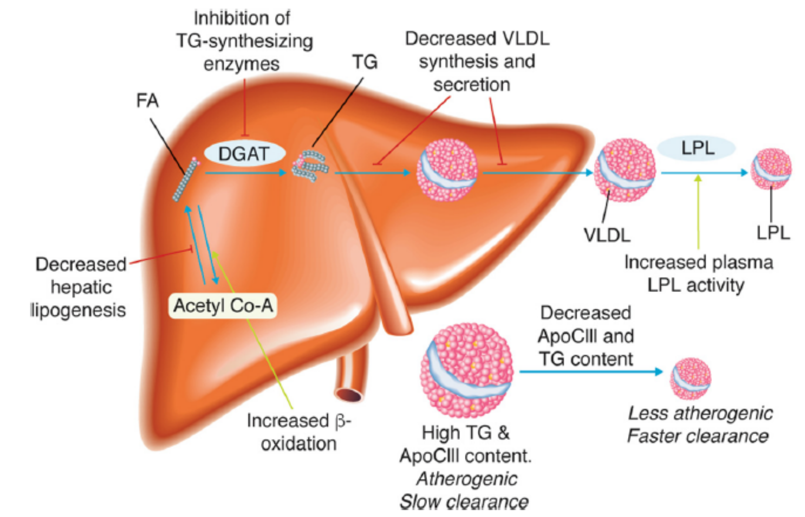


Fig. 1 Proposed mechanisms of action of prescription formulations of long-chain omega-3 fatty acids. *ApoCIII* apolipoprotein CIII, *Acetyl Co-A* acetyl coenzyme A, *DGAT* diglyceride acyltransferase; *FA* fatty acid, *LPL* lipoprotein lipase, *TG* triglyceride, *VLDL* very-low-density lipoprotein

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)

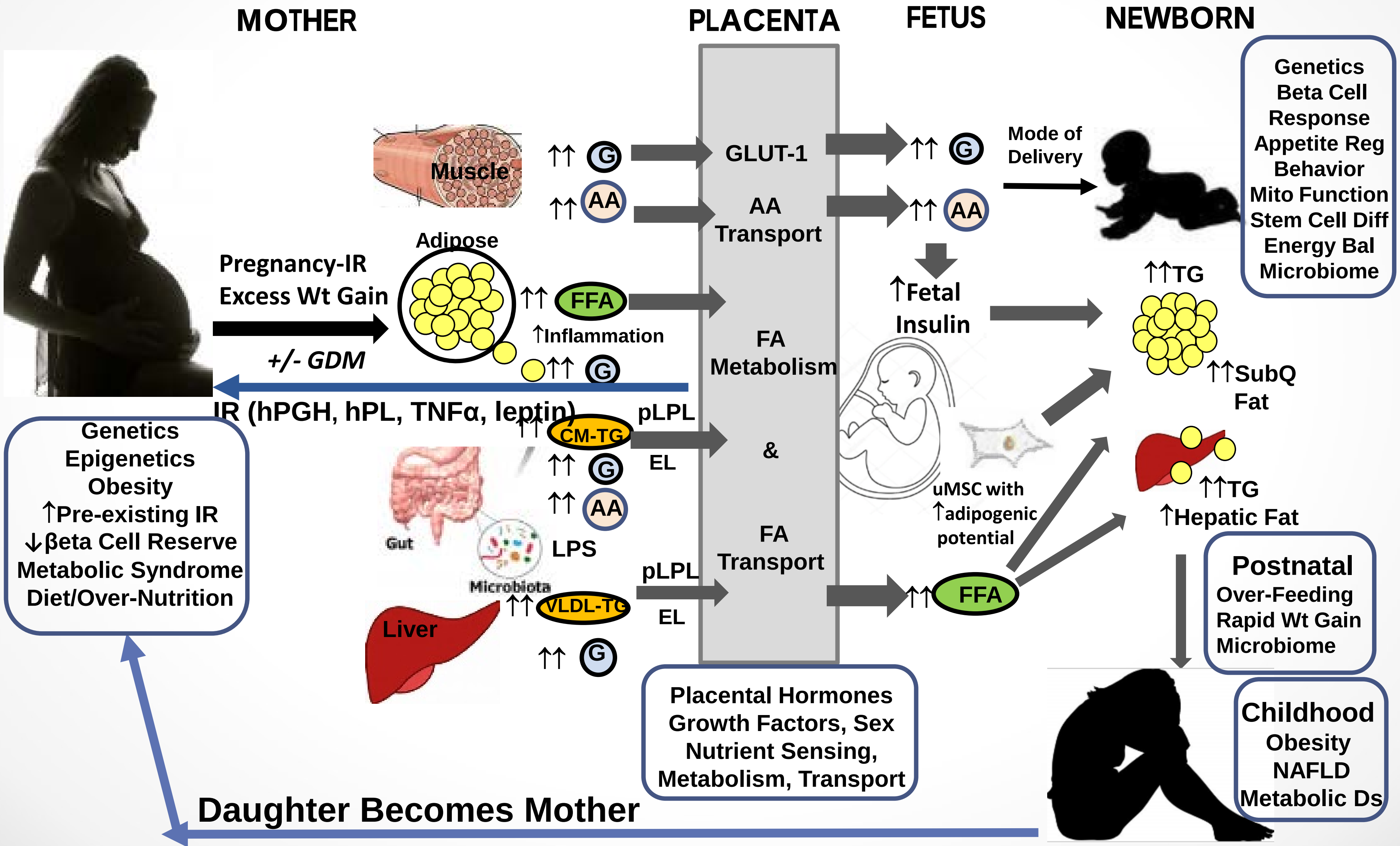
Parameter	OM3CA (Epanova) [17]			OM3EE (Lovaza) [14]		IPE (Vascepa) [16]	
	Placebo (olive oil) (*n* = 100)	OM3CA 2 g/day (*n* = 100)	OM3CA 4 g/day (*n* = 99)	Placebo (corn oil) (*n* = 42)	OM3EE 4 g/day (*n* = 42)	Placebo (mineral oil) (*n* = 75)	IPE 4 g/day (*n* = 76)
TG							
Median BL, mg/dL	682	717	655	788	816	703	680
Median percentage change from BL, %	−10	−25	−31	7	−45	10	−27

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



Barbour, Hernandez 2019

Offspring Health Starts in Utero

Obese three-year-old becomes youngest child diagnosed with Type 2 diabetes

Type 2 diabetes used to be called 'mature onset' diabetes but more and more children are being diagnosed

2K 334 0 56 2K Email

A three year old has been diagnosed with Type 2 diabetes Photo: Alamy

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

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Thanks to Moms and Babies!