IMPACT OF MATERNAL OBESITY ON PLACENTAL FUNCTION AND OFFSPRING OUTCOMES – GIVE FISH A CHANCE

March 1st, 2023

Dr. Perrie O’Tierney Ginn | Dr. Lynne Ausman
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Jordan Nutrition Innovation Lab Webinar

Impact of Maternal Obesity on Placental Function and Offspring Outcomes - Give Fish a Chance

Wednesday, March 1st, 2023
4:00-5:00 pm Jordan Time | 8:00-9:00 am US Eastern

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IMPACT OF MATERNAL OBESITY ON PLACENTAL FUNCTION AND OFFSPRING OUTCOMES – GIVE FISH A CHANCE

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@PlacentaSci
29.0% US WOMEN ARE OBESE BEFORE PREGNANCY

miscarriage

prematurity

gestational diabetes

Cesarean birth

birth defects

preeclampsia

macrosomia

NOTES: Obesity is a body mass index of 30.0 or higher. Increases from 2016 through 2019 are significant (p < 0.05). Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db392-tables.pdf.4 SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality file.
MATERNAL OBESITY INCREASES CARDIOMETABOLIC DISEASE RISK IN OFFSPRING

Typically, male offspring are at higher risk

Dearden, 2018

↑ leptin
↑ HOMA-IR
↑ inflammatory cytokines
↑ TGs
↑ FFA

Oxidative stress
Inflammation
Insulin resistance
Diet
Dyslipidemia
Vascular reactivity
Oxidative stress
1 in 4 women are obese before pregnancy... implications??

Wijendran, et al., Lipids 2000
IMPORTANCE OF FA TO THE FETUS

Cardio-metabolic consequences of essential fatty acid deficiency:

- hypertension
- vascular dysfunction
- insulin resistance/diabetes
- obesity

Weisinger, et al., Nature 2001
WHAT CONTROLS FETAL FA DELIVERY?

Maternal supply
Uptake
Metabolism/storage
Transport to fetal circulation
PLACENTAL FA DELIVERY

Effect of maternal obesity
Placental FA uptake is impaired in patients with obesity and diabetes

Fatty acid transporters and binding proteins are lower in obese human term placentas (males)

- Data from Dube 2012, Brass 2013, Araujo 2013, *(in males only)*

Pagan 2013

Adapted from Duttaroy, 2008
SUMMARY

• FA transporters and/or uptake is generally lower in placentas of obese patients

• FA transporter levels are very high in the trophoblast layer, suggesting that uptake regulation at this structure may be limited

• After uptake – what happens to the lipids?
FA METABOLISM

What does the placenta do with lipids?
PLACENTA METABOLIZES FATTY ACIDS

**FA Oxidation**
- Placenta oxidizes fatty acids even in the presence of glucose
- Drives FA uptake
- Fetuses with FAO disorders:
  - Placental insufficiency due to low ATP production → fetal growth restriction, prematurity
- Placenta FAO important for proper development of the fetal-placental unit and health of the mother

**FA Esterification**
- Protects trophoblast from lipotoxicity
- Leads to PL (structural lipids) and TG (storage) synthesis
- Placenta has lipid droplets that are sensitive to maternal nutrition/diet
- May be an essential intermediate step between uptake and delivery to fetus
- Placenta lipid pools are key to FA transfer dynamics

Rakheja, Placenta 2002; Oey, J Inherit Metab Dis, 2003; Shekhawat, AJP Endo Metab 2003; Szabo, 1973; Calabuig-Navarro, 2016; Hirschmugl 2021
MATERNAL OBESITY ALTERS PLACENTAL LIPID METABOLISM

↓ mitochondrial number in placentas of patients with obesity

MATERNAL OBESITY ALTERS PLACENTAL LIPID METABOLISM

↑ Peroxisomal contribution in FAO in placentas of women with obesity
Maternal obesity is associated with increased placental FA esterification and lipid content.
SCD1
DGAT1
PPARγ +
Mitochondrial β-oxidation
Mitochondrial number

Partial β-oxidation

COT  DBP

FA (< C8)

CPT1

Etomoxir

Lipid Esterification

LIPID DROPLET

CPT2  CACT  Cytb

β-Oxidation

MITOCHONDRIA

PALMITATE
(C16)

PPARα +
Peroxisomal oxidation
FA Esterification
Total lipid content

Calabuig-Navarro et al  Maternal Obesity and Placental Lipid Metabolism  Endocrinology, August 2017, 158(8):2543–2555
SUMMARY

• Placental FA metabolism is essential for placental function, fetal growth, and maternal health

• Mitochondrial number and β-oxidation capacity are reduced

• Peroxisomal β-oxidation capacity is greater; overall FA oxidation maintained

• FA esterification and storage pathways are increased in placentas of obese patients
The influence of placental metabolism on fatty acid transfer to the fetus

Birgit Hirschmugl 1,2, Simone Perazzolo3,4, Bram G. Sengers3,4, Rohan M. Lewis 4,5, Michael Gruber1, Gernot Desoye1, Christian Wadsack1,2

Received: 24 April 2020 / Revised: 8 January 2021 / Accepted: 1 February 2021

Placental metabolism may drive FA uptake and modify neonatal fat accrual

- The decrease in DHA mobilization from placental metabolic pool in obese women results in lower DHA levels in the fetal circulation
- Placental lipid pool is key to transfer dynamics
CAN WE MODIFY PLACENTAL FA METABOLISM?

Potential for nutritional intervention
FISH OIL SUPPLEMENTATION DURING PREGNANCY

Effect of ω-3 supplementation on placental lipid metabolism in overweight and obese women

Virtu Calabuig-Navarro, Michelle Puchowiec, Patricia Glazebrook, Maricela Haghici, Judi Minium, Patrick Catalano, Sylvie Hauguel de Mouzon, and Perrie O'Tierney-Ginn

No effect on FA oxidation

In stratified analyses, the effect of FO on FFM was strongest in obese patients, patients with high n-6/n-3 dietary intake, and those with male offspring.

*Adjusted for fetal sex and GA; β 126g, 95% CI: 3, 249
SUMMARY

- Placental FA storage and esterification pathways are sensitive to maternal omega-3 levels

- Unclear how changes in placental lipid metabolism affect fetal fat accrual

- Supplementation did not start until 14-16 weeks of pregnancy…what if it is too late?
1st TRIMESTER PLACENTA IS SENSITIVE TO MATERNAL ENVIRONMENT

#1 affected pathway was PPARα

*Adjusted for GA: avg 10 weeks (range 6-14 w)
PPARα is master regulator of lipid metabolism.

Rasool, et al. Sci Reports, 2022
N-3 FA MODULATE PLACENTAL LIPID METABOLISM

Rasool & O’Tierney-Ginn, unpublished data
EFFECT OF A HIGH OMEGA-3 ENVIRONMENT

Preconception exposure
FISH CONSUMPTION IS GREATER IN WESTERN VS MIDWEST STATES

Data from NHANES 2003-2010, EPA-820-R-14-002, April 2014
MATERNAL DHA IS HIGHER IN THE REGION OF HIGH OMEGA-3 INTAKE

Hypothesis: chronically high maternal omega-3 levels may suppress the effects of maternal obesity on placental lipid metabolism

Alvarado et al., Placenta, 2018
PLACENTAL LIPID CONTENT IS NOT DIFFERENT BETWEEN LEAN AND OBESE PATIENTS IN HAWAII

Alvarado et al., Placenta, 2018
FETAL GROWTH IN HIGH VS LOW OMEGA-3 ENVIRONMENTS
SUMMARY

• High maternal omega-3 levels may suppress effects of maternal obesity on placental lipid metabolism

• The nutritional environment is a critical consideration when studying obesity effects

• Lower neonatal leptin (a marker of fat mass) in offspring of obese patients in Hawaii compared to Ohio, suggest reduced fat accrual in utero.
QUESTIONS REMAIN

• How changes in placental lipid metabolism affect placental function and fetal fat deposition

• Chronic omega-3 consumption modifies the effect of maternal obesity on metabolic pathways…how? Whole fish vs. supplements? Do all patients benefit?

• What is the role of the maternal metabolic environment in early pregnancy on these outcomes? Are interventions starting too late?
Thank you!

Patrick Catalano, MD; Tufts
Sylvie Hauguel deMouzon, PhD; Case Western
Charles Hoppel, PhD; Case Western
Michelle Puchowicz, PhD; U of Tennessee
Stacy Tsai, MD; U Hawaii

O’Tierney-Ginn Lab BBQ, pre-COVID era
Thank you!

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Q&A
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