Effects of Maternal Obesity on the Placenta and Metabolic Changes in the Fetus

Gernot Desoye

Clinic of Obstetrics and Gynaecology, Medical University of Graz, Austria
Maternal-Fetal Supply Line

Mother
- Nutrition
- Oxygen
- Stress
- Metabolism
- Infections
- Physical Activity

Fetus
- Placenta
- Genotype
- Phenotype

Outcome
- Metabolism
- Endocrine
- Cardiovascular
- Reproduction
- Behaviour
Neonatal Phenotype in Diabesity
Maternal Obesity is Associated with More Subcutaneous Fat in the Newborn

Whitelaw AGL, BMJ 1:985, 1976

<table>
<thead>
<tr>
<th>Normal (10-90th centile) n=179</th>
<th>Obese (&gt; 90th centile) n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.6 ± 5.7</td>
<td>32.2 ± 6.1 p&lt;0.001</td>
</tr>
</tbody>
</table>
Pedersen – Freinkel Concept Expanded

Glucose

Syncytiotrophoblast

Fetal Maternal

Placenta

Endothelium

Glucose

Insulin

White adipose tissue

Growth
Total Adipocyte Cell Number is Established Early in Life and is Greater in Obese Subjects

Weight loss does not reduce adipocyte number!

Pedersen – Freinkel Concept Expanded

Glucose ➔ Lipogenesis ➔ TG ➔ Lipogenesis ➔ LPL ➔ Growth

HDL ➔ TG ➔ HDL

Glucose ➔ Insulin ➔ Growth

syncytiotrophoblast ➔ endothelium

maternal ➔ fetal

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Cord Blood Insulin Association with SAT Thickness Differences by Neonatal Sex

Boys

Total SAT thickness

Girls

Total SAT thickness

Body Fat at Birth Correlates with Body Fat at 9 Years of Age

Body fat (%)

Child Body Fat at Follow-Up (%) vs Neonatal Body Fat (%)

\[ r = 0.29, \quad P = 0.02, \quad N = 63 \]

Elevated Amniotic Fluid Insulin Associates with Obesity and IGT in Childhood


Glucose Transfer Across Term Human Placenta

Transfer characteristics:
- Rapid
- Efficient
- GLUT1

Ex vivo placental perfusion

Maternal glucose: 8 mM

D-glucose (mmol.min\(^{-1}\).total placental weight\(^{-1}\))

Control

GDM

Diet

Insulin

Osmond et al, Diabetologia 2001
Transplacental Glucose Flux at End of Gestation

Not determined at the level of the placenta

Depends on the MATERNAL-FETAL glucose concentration gradient

Clinical implications

Desoye & Nolan, Diabetologia 2016
Contribution to gradient

Maternal role

M F Placenta

Glucose ↑

Insulin ↑

Glucose ↓

Fetal role

M F Placenta

Adiposity ↑

Maternal role

M Placenta F

HG →

Fetal role

M F Placenta

HI →

HG ↓
Glucose is Taken up Faster by Neonatal Tissues in Diabetes

k-value: Blood glucose disappearance rate constant

Fetal glucose steal phenomenon

Desoye & Nolan, Diabetologia 2016
Controlling maternal blood glucose may not be enough to prevent excessive fetal fat accumulation. May blunt maternal postload glucose peaks. GDM may become unrecognized.

Fetal Hyperinsulinism Blunts Maternal Glucose Levels after oGTT

Fetal Hyperinsulinism Blunts Maternal Glucose Levels after oGTT

At what Time in Gestation Can Fetal Hyperinsulinism Begin?
Insulin in Human Fetal Pancreas

In t' Veld Diabetologia 35, 272 (1992)
AF Insulin Present at 14-20 wks Gestation
(n=247)

Higher AF insulin (by 1 MOM) associated with 3-fold risk for birth weight > 90th centile

Carpenter MW Diabetes Care 24: 1259 (2001)
First-Trimester Fasting Glycemia Correlates with Neonatal Weight

6129 women

Median GA at fasting glucose: 9.5 weeks

Riskin-Mashia S et al Diabetes Care 32: 1639, 2009
First-Trimester Fasting Glycemia Correlates with Neonatal Weight

6129 women

Median GA at fasting glucose: **9.5 weeks**

Riskin-Mashia S et al Diabetes Care 32: 1639, 2009
Placental Volume (wks 11-14) Associates with Birth Weight Category

Effendi M et al
Placenta 35:99–102, 2014

Plasencia W et al
Fetal Diagn Ther 30:23-28, 2011
Insulin Response (IVGTT) and Placental Weight

Pre-pregnancy

Early pregnancy (12-14 weeks)

Late Pregnancy (34-36 weeks)

R=0.42, P=0.007

R=0.26, P=n.s.

R=0.08, P=n.s.

O’Tierney-Ginn et al, JCEM, 2015
Maternal – Placental – Fetal Dialogue

*Desoye & van Poppel, 2014*

**Insulin**

**Glucose**

**Placenta**

placental development

**Hypothalamus**

Adipocytes number

TG deposition

**ß-cell changes**

**Diabetes risk**

First trimester → 2nd & 3rd trimester

Pregnancy

Childhood Adulthood
Maternal – Placental – Fetal Dialogue

Debye & van Poppel, 2014

**Insulin resistance**

- Obesity
- IGT/T2D
- Stress
- Environmental pollutants

**Glucose**

- Insulin

**Placenta**

- Adipocytes
- TG deposition
- Hypothalamus
- β-cell changes

First trimester → 2nd & 3rd trimester

Pregnancy
Diabetes in pregnant women shall be carefully managed in early gestation in the hope of preventing excessive body fat deposition in the conceptus.

Thank you!
Extra slides

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Fetal Fat Lobules Detected at Week 14

Fat Lobule Size (µm)

Crown Rump Length (mm)

r = 0.822

## Early Changes in Plasma Glucose Concentration by BMI

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<td>-0.78</td>
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*6-12 wks*

*Mills et al Metabolism 47, 1140-44; 1998*
Neonates born to obese GDM mothers have more intrahepatocellular fat

Cord Blood C-Peptide Correlates with 1st Trimester Maternal BMI

Insulin release by human islet-like cell cultures (ICC)

Insulin Secretion from Human Fetal Pancreata

Basal Insulin Secretion

Reiher et al, Diabetes Care 6:446, 1983
Fetal iGTT in subhuman primates

139-151 days; full term: 164 days

Fetal insulin [ng/ml]

Time after injection [min]

250 mg glucose

STZ diabetic animals

controls

JCI 48, 176 1969; 51, 837, 1972
Pedersen – Freinkel Concept Expanded

Glucose

Lipogenesis

Liver

HDL

LPL

TG

White adipose tissue

Growth

Insulin ↑

maternal

fetal

syncytiotrophoblast

endothelium

Glucose

Insulin ↑
EL is Upregulated by GDM plus Obesity

Endothelial lipase is upregulated in obese GDM only

Inflammatory cytokines upregulate placental EL

Gauster et al; Diabetes 2011
Free fatty acid (1-3%) is associated with albumin complex. After dissociation, free fatty acids (97-99%) are transported by lipoproteins. Oxidation occurs in mitochondria and peroxisomes. Biological activity involves signal transduction, gene regulation, and eicosanoid formation. Fatty acid binding protein (FABP) facilitates lipid resynthesis and storage in lipid droplets. Fatty acid transport protein (FATP) and FAT/CD36 play roles in diffusion and lipid hydrolysis. Lipoprotein receptor facilitates the entry of lipoproteins. Fetal liver incorporates free fatty acids into lipoproteins. α-fetoprotein is associated with storage in lipid droplets. Desoye & Herrera, 2016.
Fatty Acid Transfer Across Term Human Placenta

Transfer characteristics:

- Slow (3% clearance of H₂O)  
  * * * Placenta 18: 635, 1997
- Inefficient
- Dependent on chain length
- Maternal FAs contribute to only ~70g (20%) of neonatal fat (normal pregnancy)  
  * * * Pediatr Res 7:192, 1973

In vivo stable isotopes

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<th>Enrichment in fetal circulation (% of maternal)</th>
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<tr>
<td>3</td>
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<td><strong>13C-PA</strong> (16:0)</td>
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Pagán A et al, AJP-Endocr Metab 2013
DHA Transfer is More Efficient than Transfer of Non-essential FAs

*Ex vivo placental perfusion*

**Essential FA**

**Non-essential FA**

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<td>13C-DHA (22:6)</td>
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DHA Transfer is More Efficient than Transfer of Non-essential FAs

Hirschmugl et al, unpublished
**FA Composition of Adipose Tissue in Neonates is Unaltered in Diabetes**

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<th>Fatty Acid (% of Total)</th>
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*King et al, Pediatrics; 47:192-198, 1971*
Modelling of Perfusion Data Suggest: Two Placental Fatty Acid Pools

- Slow high capacity route via metabolic pools (e.g., phospholipids)
- Fast low capacity route

Relatively high transfer from mother to fetus

Relatively low transfer from fetus to mother

Placenta has limited capacity to store excess fatty acids in obesity

Proposed Mechanism

Modelling of Perfusion Data Suggest: Two Placental Fatty Acid Pools

Slow high capacity route via metabolic pools e.g. phospholipid

Relatively high transfer

Fast low capacity route

Relatively low transfer

Only DHA Transfer is Altered by Maternal Obesity

**Ex vivo placental perfusion**

- **Non-essential FA**
  - $^{13}$C-PA (16:0)
  - $^{13}$C-OA (18:1)
  - $^{13}$C-LA (18:2)

- **Brain:** 4.1%
- **Adipose Tissue:** 1.6%
- **Plasma:**
  - PL 6.6%
  - TG 1.6%
  - CE 1.1%
  - NEFA 2.8%

Hirschmugl et al, unpublished

Haggarty P, Eur J Clin Nutr 2004
Fatty Acids in Umbilical Cord Plasma

Ortega-Senovilla H et al, Diabetes Care 2009
Low Cord Plasma DHA Levels May Indicate Fetal Insulin Resistance

Summary Fatty Acids

- Obesity does not Affect Transplacental Transfer of Non-essential Fatty Acids
- Obesity enhances DHA Transfer
- Does obesity enhance DHA extraction into fetal tissues
  - Is this an insulin driven phenomenon?
- Consequence: fetal DHA steal?

(Desoye & Nolan Diabetologia, 2016)
Umbilical cord C-peptide associated with arterial stiffness at 15 years

N= 129/42 GDM; 87 controls; no difference

C-peptide: < or ≥ 75 percentile

Fetal hyperinsulinism leads to multiple changes

- Vascularization
- Glucose uptake
- Metabolism
- Liver / Skeletal muscle
- Proliferation
- TG storage
- Adipocyte
- Growth
  - Orexigenic
    - NPY/ AGRP
    - ARC neurons
  - Differentiation
    - Anorexigenic
      - Ventromedial nucleus
- Brain/Hypothalamus
- Growth
  - Orexigenic
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    - ARC neurons
  - Differentiation
    - Anorexigenic
      - Ventromedial nucleus

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Mills et al Metabolism 47, 1140-44; 1998
Summary - Glucose

The placenta does not appear to actively contribute to fetal oversupply with glucose (at the end of gestation)
Summary

Late in pregnancy:

- Glucose transfer driven by maternal-fetal concentration gradient
- Mechanisms of lipid/fatty acid transfer unclear
- No evidence for direct contribution of placenta to fetal overnutrition (maternal diabetes, obesity)
Maternal – Placental – Fetal Dialogue

Desoye & van Poppel, 2014

First trimester

Placental development

2nd & 3rd trimester

Pregnancy

Childhood

Adulthood

Diabesity risk

Insulin

Glucose

Adipocyte number

TG deposition

Hypothalamus

β-cell changes

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Special Role of DHA in Materno-Fetal Dialogue

• Transfer mechanism

• Fetal/neonatal insulin sensitivity
Special Role of DHA in Materno-Fetal Dialogue

- Transfer mechanism
- Fetal/neonatal insulin sensitivity
- Fetal/neonatal brain development
Cord DHA Associates with Psychomotor Development Index (PDI) at 6 months

Dissociation

1-3% FA Albumin Complex

Free fatty acid

EL

97-99% FA Lipoproteins

FABPpm

Lipoprotein Receptor

FAT/CD36

Lipid hydrolysis

Lipid resynthesis

FAS

Fatty Acid Synthase

FATP

Free fatty acid

Fetal liver:

Incorporation into Lipoproteins

α-fetoprotein

Storage in Lipid Droplets

Desoye & Herrera, 2016
Lipids

- Free fatty acids (1-3%)
- Lipoproteins
  - Apoproteins
  - Cholesterol/esters
  - Triglycerides
  - Phospholipids
  - Vitamins
Tree-like Structure of Human Placenta
The human placenta is compartmentalized.
Compartimentalization of Fatty Acid Utilization

Fatty acids

diffusion

stroma

FA-CoA

conversion

oxidation

elongation

desaturation

triglyceride synthesis

Fatty acids

transporters-ligases

Fatty acids

diffusion
Obesity Effect on 90 Placental Target Genes Related to Lipids

Maternal Glucose is Essential for Fetal Development

The fetus does not produce glucose.

The fetus requires ~ 40 g glucose per day.

Placental GLUT1 is major glucose transporter for transfer.
GLUT 1 in Term Placentas

Hahn et al, Cell Tiss Res 1995
Placental Glucose Transporters in vitro Regulation

Hyperglycemia in vitro downregulates glucose uptake and GLUT1 in human term trophoblasts

Hahn et al., FASEB J 12: 1221, 1998

Hyperglycemia in vitro induces GLUT1 translocation in term human trophoblasts

Hahn et al., Diabetologia 43: 173, 2000
Transplacental glucose transport depends on maternal and fetal blood flow

Maternal blood flow

Fetal blood flow

Illsley et al, Trophoblast Res 1987
Determinants of Materno-Fetal Transfer

- Structure and morphology
- Metabolism
- Transport activity

Mother → Concentration gradient → Fetus

Utero-placental blood flow

Umbilical blood flow
TG and acetyl coA carboxylase activity in human fetal subcutaneous tissue


![Graph showing TG and Acetyl CoA carboxylase activity across gestational age](image)

Body Fat (%) in Offspring of Women with GDM and Obesity

Petersen 1988; Catalano AJOG 2003; Durnwald AJOG 2004; Sewell AJOG 2006
Triglycerides in Placental Tissue

lean (20-25 kg/m² n=18) vs. obese (30-64 kg/m² n=55), placenta specimen collected in Cleveland (USA)

* P <0.05, *** P <0.001

Maternal BMI and Insulin Associate with Placental CGI-58

Villus tree is made up by various types of villi with different functions.
Human Newborns have Highest % Body Fat among Mammals

Kuzawa CW, Yearbook Physical Anthropol 1998
Maternal and Fetal Fat During Gestation

Fetal lipid accretion maximum at term of gestation: 7 g/day

EM Widdowson, 1968; P Haggarty, Ann Rev Nutr 2010
The Human Term Placenta

Rohan Lewis & MuVis, University of Southampton
The human placenta is compartmentalized.

Lewis et al
Ann Nutr Metab 63:208, 2013

Courtesy Dr C. Jones, Univ Manchester, UK
Pedersen – Freinkel Concept Expanded

Glucose

Lipogenesis

TG

Liver

Insulin ↑

HDL

TG

White adipose tissue

LPL
FA Transfer is not Altered by Maternal Obesity

Ex vivo placental perfusion

Non-essential FA

Enrichment in fetal effluent (% of maternal)

BMI <25 kg/m²

BMI >30 kg/m²

13C-PA (16:0)
13C-OA (18:1)
13C-LA (18:2)

Hirschmugl et al, unpublished
Fetal Hyperinsulinism May Stimulate Extraction of Polyunsaturated Fatty Acids
The Placenta has Two Surfaces which Interact with the Environment of Mother and Fetus

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Computer Model Predicts Transfer

Lewis R et al,
Southampton, UK
Compartimentalization of Fatty Acid Utilization

**Metabolism**

\[ \text{FA} \xrightarrow{\text{FATP}} \text{FA} \xrightarrow{\text{FATP}} \text{Acyl-CoA} \xrightarrow{\text{Storage, Conversion, Oxidation}} \]

**Transfer**

\[ \text{FA} \xrightarrow{\text{Diffusion}} \text{FA} \xrightarrow{\text{FA:FABP}} \text{FA} \xrightarrow{\text{Diffusion}} \text{FA} \]
Gestational Changes in Maternal and Fetal Lipids

Desoye G et al. JCEM 1987

P. Haggarty Ann Rev Nutr 30:237, 2010
Total Transplacental Net Transfer of Glucose

Maternal glucose: 8 mM

Control

GDM

D-glucose (mmol.min⁻¹.total placental weight⁻¹)

Diet

Insulin

Osmond et al, Diabetologia 2001
Term Placenta

GLUT3

Mol Hum Reprod 2001 7:1173

GLUT4

JCEM 1998 83:4097
Placental Glucose Utilisation

Desoye & Shafrir 1994

Mother

Fetus

Glucose

Glycogen

Triglyceride

FA

Glycerol

Lactate

CO₂

2% 3% 10%

80%

5%
Placental glucose consumption

Glucose uptake and transfer depend on maternal-fetal concentration gradient

Maternal-fetal glucose transfer is unaltered in FGR

Experimental Period

Glucose transfer (µmol min⁻¹ g⁻¹)

Preterm FGR

Preterm normal

Term normal

Transfer routes for maternal nutrients and oxygen

SEM of terminal villus

Charnock-Jones DS & Burton G
Baillière’s Clin Obst Gyn 14:953, 2000
Nutrient transfer across the placenta: Oxygen
Human Newborns have Distinct Features among Mammals

Cerebral O₂ uptake
(% of total body metabolism)

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Kuzawa CW. Yearbook Physical Anthropol 41:177-209, 1998
The fetus can be Hypoxic in GDM

Umbilical erythropoietin levels

P<0.01

Control (16)  GDM (20)

White A & A/B

Fetal Hyperinsulinism Contributes to Hypoxia
The Placenta in Diabetes is Hypervascularized

So-called monster villus, diabetes mellitus, wk 40

(Desoye, Kaufmann 2005)
Fetal Hypoxia and Insulin Stimulate Vascularization

compartment

maternal stroma fetal

syncytiotrophoblast endothelium

↑ glucose glucose ↑
Adipocyte ↑
Glucose uptake
insulin ↑

VEGF

oxygen ↓
Metabolism ↑
## Diffusion-dependent transport in diabetes

<table>
<thead>
<tr>
<th>Oxygen</th>
<th>Diffusive conductance (ml/min.kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>29 ± 1.4</td>
</tr>
<tr>
<td>White A-C</td>
<td>36 ± 1.8*</td>
</tr>
<tr>
<td>White D,F,R</td>
<td>31 ± 1.6*</td>
</tr>
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*Mayhew et al. Diabetologia 36, 955, 1993*
Fetal Phenotype in Diabetes

Catalano AJOG 2003; Durnwald AJOG 2004; Whitelaw AGL, 1976

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<th>Body Fat (%)</th>
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<td>Obese (&gt; 90th centile)</td>
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<th>LGA</th>
<th>AGA</th>
<th>SGA</th>
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Pedersen – Freinkel Concept Expanded

Glucose

Insulin ↑

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maternal

Glucose

Lipoproteins

FFA

syncytiotrophoblast

endothelium

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White adipose tissue

Pedersen – Freinkel Concept Expanded

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Fetal lipid accretion maximum at term of gestation:

7 g/day

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Haggarty P Ann Rev Nutr 30:237, 2010
Lipids

- Free fatty acids (1-3%)

- Lipoproteins
  - Apoproteins
  - Cholesterol/esters
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  - Phospholipids
  - Vitamins
Hydrolysis by Lipases

1-3% FA Albumin Complex

Free fatty acid

97-99% FA Lipoproteins

Dissociation

Lipoprotein Receptor

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EL is Upregulated by GDM plus Obesity

Endothelial lipase is upregulated in obese GDM only

Inflammatory cytokines upregulate placental EL

Gauster et al. Diabetes, 2011
**Oxidation**
- Mitochondria
- Peroxisomes

**Biological activity**
- Signal transduction
- Gene regulation
- Eicosanoid formation

**Free fatty acid**

**Lipoprotein Receptor**

**Dissociation**

**FATP**

**FABP**

**FAT/CD36**

**EL**

**Storage in Lipid Droplets**

**Lipid resynthesis**

**Incorporation into Lipoproteins**

**1-3% FA**

**Albumin Complex**

**97-99% FA Lipoproteins**

**Diffusion**
Fatty Acid Transfer Across Term Human Placenta

Transfer characteristics:

- Slow (3% clearance of H_2O)
  *Placenta 18: 635, 1997*
- Inefficient
- Dependent on chain length
- Maternal FAs contribute to only ~70g (20%) of neonatal fat (normal pregnancy)
  *Pediatr Res 7:192, 1973*

*In vivo stable isotopes*

Enrichment in fetal circulation (% of maternal)

- **13C-PA** (16:0)
- **13C-OA** (18:1)
- **13C-LA** (18:2)
- **13C-DHA** (22:6)

*Pagán A et al, AJP-Endocr Metab 2013*
FA Transfer is not Altered by Maternal Obesity

Ex vivo placental perfusion

Enrichment in fetal effluent (% of maternal)

- BMI <25kg/m²

Non-essential FA

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<td>C 16:1</td>
<td>13.3 ± 3.0</td>
<td>14.0 ± 2.2</td>
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<tr>
<td>C 18:0</td>
<td>5.7 ± 2.3</td>
<td>3.8 ± 1.1</td>
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<tr>
<td>C 18:1</td>
<td>24.8 ± 2.5</td>
<td>28.0 ± 5.2</td>
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<tr>
<td>C 18:2</td>
<td>1.1 ± 1.1</td>
<td>1.0 ± 1.1</td>
</tr>
</tbody>
</table>
Pedersen – Freinkel Concept Expanded

Glucose

Lipogenesis

TG

Liver

HDL

White adipose tissue

FFA

EL

LPL

Syncytiotrophoblast

Maternal

Fetal

Placenta

Endothelium

Pedersen – Freinkel Concept Expanded

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia.

Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
Only DHA Transfer is Altered by Maternal Obesity

Ex vivo placental perfusion

Hirschmugl et al, unpublished

Brain: 4.1%

Plasma:
- PL 6.6%
- TG 1.6%
- CE 1.1%
- NEFA 2.8%

Adipose Tissue: 1.6%

Haggarty P
Eur J Clin Nutr 58:1559-1570, 2004
Fatty Acids in Umbilical Cord Plasma

Ortega-Senovilla H et al Diabetes Care 32: 120, 2009
Fetal Hyperinsulinism May Stimulate Extraction of Polyunsaturated Fatty Acids

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia.

Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
Computer Model Predicts Transfer

Lewis R et al,
Southampton, UK
Villus tree is made up by various types of villi with different functions

Compartimentalization of Fatty Acid Utilization

**Fatty acids**
- **diffusion**

**stroma**

**FA-CoA**

**triglyceride synthesis**

**conversion**

**oxidation**

**elongation**

**desaturation**

**Fatty acids**
- **transporters-ligases**

---

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
Compartimentalization of Fatty Acid Utilization

Metabolism

FATP

FA $\xrightarrow{\text{FATP}}$ FA $\xrightarrow{\text{FATP}}$ Acyl-CoA $\xrightarrow{\text{Storage, Conversion, Oxidation}}$

Transfer

FA $\xrightarrow{\text{Diffusion}}$ FA $\xrightarrow{\text{FA:FABP}}$ FA $\xrightarrow{\text{Diffusion}}$

www.project-earlynutrition.eu
Nature of the metabolic pool?

How does the placenta handle the fatty acid excess of GDM & obesity?
Human placenta contains lipid bodies in the syncytiotrophoblast


Shafrir et al, AJOG 144: 5, 1982
Cleveland Cohort with Various Degrees of Obesity

RNA extracted
Quality control on bioanalyzer, RIN>7.5
Gene expression measured by Nanostring technology

<table>
<thead>
<tr>
<th>BMI</th>
<th>Number of samples</th>
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<tbody>
<tr>
<td>Lean: 20-24.9</td>
<td>20</td>
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<tr>
<td>Obese: 30.0-33.9</td>
<td>24</td>
</tr>
<tr>
<td>34.0-39.9</td>
<td>16</td>
</tr>
<tr>
<td>≥ 40.0</td>
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Pathways and Genes examined

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Number of Genes</th>
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<tbody>
<tr>
<td>House keeping genes</td>
<td>34</td>
</tr>
<tr>
<td>Lipid and FA uptake/binding</td>
<td>16</td>
</tr>
<tr>
<td>Lipid storage</td>
<td>5</td>
</tr>
<tr>
<td>Lipases/Hydrolases</td>
<td>11</td>
</tr>
<tr>
<td>FA elongation/desaturation/oxidation</td>
<td>16</td>
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<tr>
<td>Hormones and hormone receptors</td>
<td>5</td>
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<tr>
<td>Lipoprotein associated proteins</td>
<td>11</td>
</tr>
<tr>
<td>Transcription factors/regulators</td>
<td>8</td>
</tr>
<tr>
<td>Cholesterol and Steroid Hormone Transport/Biosynthesis</td>
<td>18</td>
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<tr>
<td></td>
<td>90</td>
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</tbody>
</table>
Correlation of Maternal BMI with Lipid Related mRNAs in Placenta

N=80; 90 targets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
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<th>Female</th>
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<td></td>
<td>r</td>
<td>p-value</td>
<td></td>
<td>r</td>
<td>p-value</td>
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<tr>
<td>ACAT1</td>
<td>-0.189</td>
<td>0.213</td>
<td></td>
<td>-0.144</td>
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<tr>
<td>ACAT2</td>
<td>-0.164</td>
<td>0.201</td>
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<td>-0.421</td>
<td>0.012</td>
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<tr>
<td>CGI-58</td>
<td>-0.119</td>
<td>0.438</td>
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<td>-0.366</td>
<td>0.031</td>
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<tr>
<td>PLIN 2</td>
<td>0.237</td>
<td>0.117</td>
<td></td>
<td>0.296</td>
<td>0.084</td>
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<tr>
<td>ApoE</td>
<td>-0.148</td>
<td>0.333</td>
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<td>-0.393</td>
<td>0.019</td>
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<tr>
<td>ELOVL 1</td>
<td>-0.230</td>
<td>0.129</td>
<td></td>
<td>-0.205</td>
<td>0.237</td>
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<tr>
<td>PPARG</td>
<td>0.265</td>
<td>0.078</td>
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<td>0.280</td>
<td>0.104</td>
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</tr>
</tbody>
</table>

Spearman Correlation

www.project-earlynutrition.eu
Location of LD-associated Proteins in Human Term Placenta

Hirschmugl B et al, Int J Obes, in press
Regression of placental lipid related mRNAs with % neonatal fat

$A-FABP/FABP-4: 0.084\pm 0.037$

$FATP-2: 0.046\pm 0.029$

Adjusted for maternal smoking and fetal sex
maternal obesity

Lipids/ Fatty acids

Metabolism transfer

Fetal adiposity

Fatty acids

mother placenta foetus
Summary and Conclusion

Maternal-fetal transfer of non-essential fatty acids is unaltered in GDM and obesity

Fatty acids are stored as TG in the placenta (trophoblast) in lipid droplets; more TG stored in GDM and obesity

Activity of TG synthesis and lipolysis determine the net amount of TG stored

It is unclear what happens in extreme conditions of maternal overnutrition
<table>
<thead>
<tr>
<th>University of Southampton, UK</th>
<th>University of Murcia, ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rohan Lewis</td>
<td>Antonio Gázquez García</td>
</tr>
<tr>
<td>Simone Perazzolo</td>
<td>Elvira Larque</td>
</tr>
<tr>
<td>Bram Senger</td>
<td></td>
</tr>
<tr>
<td>Keith Godfrey</td>
<td></td>
</tr>
<tr>
<td>Sarah Crozier</td>
<td>University of Granada, ES</td>
</tr>
<tr>
<td></td>
<td>Cristina Campos</td>
</tr>
<tr>
<td></td>
<td>Maite Segura</td>
</tr>
<tr>
<td>University of Cleveland, OH, USA</td>
<td>King's College London, UK</td>
</tr>
<tr>
<td>Pat Catalano</td>
<td>Lucilla Poston</td>
</tr>
<tr>
<td>Sylvie Hauguel De Mouzon</td>
<td></td>
</tr>
</tbody>
</table>
The Team

Christian Wadsack

Eva Kitzinger

Birgit Hirschmugl
Funding:

European Commission
Thank you for your attention!
Pedersen – Freinkel Concept Expanded

Glucose

Lipogenesis
TG
Liver
HDL
TG
LPL

White adipose tissue

Insulin ↑

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
DHA is enriched in placenta and cord blood 12 hr after maternal $^{13}$C-FA administration

***Gil-Sánchez A et al., Am J Clin Nutr 92:115, 2010***

Cord blood/ Maternal

Placenta/ Maternal

---

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia.
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GlucoseInsulin↑

Glucose

Lipogenesis

TG

Liver

HDL

White adipose tissue

FFA

Lipoproteins

FFA

EL

LPL

Pedersen – Freinkel Concept Expanded

syncytiotrophoblast

endothelium

maternal

fetal

P

L

C

A

T

N

Pedersen – Freinkel Concept Expanded

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia.

Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it
Villus tree is made up by various types of villi with different functions.
Regression of Placental Lipid Related mRNAs with % Neonatal Fat

- A-FABP/FABP-4: 0.084
- FATP-2: 0.046

Adjusted for maternal smoking and fetal sex.
The role of maternal lipids in driving fetal fat accretion is still unknown.
Regression of Placental Lipid Related mRNAs with % Neonatal Fat
In Maternal Obesity the Human Placenta Stores More Triglycerides


Late Pregnancy

Diapositiva preparata da GERNOT DESOYE e ceduta alla Società Italiana di Diabetologia.
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Nutrient transfer across the placenta:

Glucose
Pathways of Materno-Fetal Transport

Glucose:
* $[\text{gluc}]_m > [\text{gluc}]_f$
* saturable
* stereospecific
* Na-indep.
* GLUT1
* mvm:bm $\sim 3:1$
Nutrient transfer across the placenta:

Lipids – Fatty Acids
The Placenta Stores Glucose

Desoye et al., Diabetologia 1994

Br J Ob Gyn 83: 43 (1976)
Fetal glucose can be stored in the placenta.
Only the placenta has the capacity to store excess fetal glucose.
The human placenta contains more DNA and stores glycogen and lipids in diabetes.
Lipids - Fatty Acids
Placental distribution of AA taken up

Kuhn et al. Diabetes 39, 914 (1990)
Type-I increases AA uptake and conversion into eicosanoids resulting in a lower PGI₂/TxA₂

Placenta is Robust to Maternal Obesity

N=90 Lipid related genes

Cleveland cohort: 6 modified (BMI)  
Hirschmugl et al., Int. J. Obes. 41:317-323, 2017

SWS cohort: 4 modified (BMI)  
Lewis R et al, in prep

---------------------------------------------------------------

N=17 Candidate genes

UPBEAT cohort: 17 genes, 1 modified  
Gill C et al, in prep

NIGO-Health cohort: 17 genes, ???? modified
Effects of a diabesogenic environment on early placental development

Lower levels of human placental lactogen in T1DM in the first trimester

High glucose levels reduce proliferation of first trimester trophoblasts in vitro
(Fröhlich et al, Am J Pathol 2012)

Insulin and TNFα upregulate MMP14 in first trimester trophoblasts in vitro
(Hiden et al, Diabetes 2008)