Regulatory Role of the Placenta in Materno-Fetal Nutrient Transfer

Kick-off Meeting, March 21-23, 2012
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This project receives funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 289346
The Human Placenta

*Moe et al, 1995; Rossant & Cross Nature Rev Gen 2001*
Placental growth precedes foetal growth

% of weight at 40 wk

weeks of gestation

Hendricks Obstet Gynecol 24:357, 1964
Foetal and placental weight correlate

1g placenta tissue sustains:

- Human: 6 g
- Rat/Mouse: 10 g
- Sheep: 10 g
- Guinea Pig: 20 g

Foetal anthropometric parameters* directly associated with:

- Placental volume at week 14 of gestation
- Rate of placental growth between week 14 and 17 of gestation

*abdominal circumference, femoral length, head circumference, biparietal diameter

Thame et al Eur J Clin Nutr 58: 894, 2004
Body Composition at Delivery

- Fat mass: 12 – 15 %
- Fat free mass: 85 – 88 %
Body Fat (%) in Offspring of Women with GDM and Obesity

Petersen 1988; Catalano AJOG 2003; Durnwald AJOG 2004; Sewell AJOG 2006
Foetus in Diabesity

characterised by:

Fat Free Mass:  Diabesity ~ control

Fat Mass:  Diabesity > control

Kehl et al. 1996; Petersen 1988; Catalano AJOG 2003; Durnwald AJOG 2004, Sewell AJOG 2006
Foetal Body Fat is Reduced in FGR

Fat mass

Lean body mass

FGR:
- Fetal AC < 2 SD
- Abnormal Doppler:
  - A. umbilicalis
  - A. uterina

Padoan et al, AJOG 2004
Foetal Growth

- Fat Free Mass / Lean Body Mass
- Genes
- Fat Mass
- Intrauterine Environment

Moulton; J Biol Chem, 1923
Sparks; Sem in Perinat, 1989
THE ‘FUEL-MEDIATED’ TERATOGENESIS CONCEPT

MOTHER

PLACENTA

FETUS

↑ Glucose
↑ Amino acids
↑ FFA

↑ Glucose
↑ Amino acids
↑ FFA

↑ Glucose
↑ Amino acids
↑ FFA

Increase in substrate utilization
Growth
Energy storage
Fat deposition

White adipocytes
Foetal hyperinsulinism

compartment

maternal

stroma

fetal

↑ glucose

glucose ↑

syncytiotrophoblast

endothelium

insulin ↑
AF insulin at 14-20 wks gestation  
(n=247)

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

OR 3.1  

[95% CI: 1.3-4.9; P=0.048]  

Carpenter MW Diabetes Care 24: 1259, 2001
Third trimester amniotic fluid insulin & childhood growth at age 6

Symmetry index = \frac{\text{Observed weight/median for age}}{\text{Observed height/median for age}}

Foetal hyperinsulinism

Compartments

Maternal

Syncytiotrophoblast

Fetal

Endothelium

↑ glucose

↑ glucose

↑ insulin
Nutrient transfer across the placenta:

Glucose
The foetus requires ~ 40 g glucose per day

The foetus does not produce glucose
Pathways of Materno-Foetal Transport

Glucose:

- $[\text{gluc}]_m > [\text{gluc}]_f$
- *saturable*
- *stereospecific*
- *Na - indep.*
- *GLUT1*
- *$\text{mvm:bm} \sim 3:1$*
GLUT 1 in Term Placentas

Hahn et al, Cell Tiss Res 280, 1995
Term Placenta

GLUT3

GLUT4

Mol Hum Reprod 2001 7:1173

JCEM 1998 83:4097
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
Total transplacental net transfer of glucose

Maternal glucose: 8 mM

Osmond et al, Diabetologia 2001
Glucose uptake and transfer depend on maternal-fetal concentration gradient

Transplacental glucose transport depends on maternal and foetal blood flow

Ilsley et al. Trophoblast Res. 2: 535, 1987
Transplacental Glucose Flux

Depends on the MATERNAL-FOETAL concentration gradient

Is flow limited
Fetal hyperinsulinism leads to multiple changes

- Adipocyte $\uparrow$
- Glucose uptake $\uparrow$
- Metabolism $\uparrow$
- Insulin $\uparrow$

Glucose steal

- $\uparrow$ glucose
- $\downarrow$ glucose

compartmentst

- maternal
- stroma
- fetal
Foetal Hyperinsulinism – A Vicious Circle

Hyperinsulinism
Nutrient transfer across the placenta:

Lipids – Fatty Acids
Maternal and Foetal Fat During Gestation

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

*EM Widdowson, 1968; P Haggarty Ann Rev Nutr 30:237, 2010*
Gestational Changes in Maternal and Foetal Lipids

Desoye G et al. JCEM 1987

P. Haggarty Ann Rev Nutr 30:237, 2010
Dissociation
Free fatty acid
Hydrolysis by Lipases

Lipoprotein Receptor

1-3% FA Albumin Complex
97-99% FA Lipoproteins
Placental EL is downregulated in FGR and upregulated in obese GDM

Inflammatory cytokines upregulate placental EL

Gauster et al. Diabetes 60: 2457, 2011
Selective FA contribution to foetal NEFA and cholesteryl ester pools

Free fatty acid

1-3% FA Albumin Complex

Dissociation

Free fatty acid

Oxidation
- Mitochondria
- Peroxisomes

Biological activity
- Signal transduction
- Gene regulation
- Eicosanoid formation

FABP

Free fatty acid

Lipid resynthesis

Storage in Lipid Droplets

FATP

FAT/CD36

Diffusion

97-99% FA Lipoproteins

Incorporation into Lipoproteins

FABPpm

EL
Human placenta contains lipid bodies in the syncytiotrophoblast


Shafrir et al, AJOG 144: 5, 1982
Oxidation

- Mitochondria
- Peroxisomes

Biological activity

- Signal transduction
- Gene regulation
- Eicosanoid formation

FABP

Free fatty acid

FATP

FAT/CD36

Lipid resynthesis

Lipid hydrolysis

Storage in Lipid Droplets

Incorporation into Lipoproteins

FABPpm

Dissociation

1-3% FA Albumin Complex

97-99% FA Lipoproteins

EL

Diffusion

Mitochondria

Peroxisomes

Lipoprotein Receptor

Free fatty acid

Diffusion

Mitochondria

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Peroxisomes

Lipoprotein Receptor

Free fatty acid

FATP

FAT/CD36

Diffusion

Mitochondria

Peroxisomes

Lipoprotein Receptor

Free fatty acid
LCPUFA are enriched in foetal plasma

Maternal plasma  Foetal plasma

![Graph showing the concentration of various fatty acids in maternal and foetal plasma](image)

- **18:2 n-6**
- **20:4 n-6**
- **22:6 n-3**

*Innis S, Placenta 26 Suppl A:S70, 2005*
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*
Fatty acids in umbilical cord plasma

PUFA

Saturated Fatty Acids

Ortega-Senovilla H et al. Diabetes Care 32: 120, 2009
Foetal hyperinsulinism may stimulate extraction of polyunsaturated fatty acids.
Nutrient transfer across the placenta:

Lipids – Cholesterol
Cholesterol

• Cell membrane constituent
• Stored in lipid droplets/bodies
• Synthesis of steroid and oxysterols
• Regulation of development (shh modification)
Maternal Hypercholesterolemia Enhances Fatty Streak Formation in Foetal Aortas

Intimal Lipid Accumulations in Foetal Aortas

Cumulative area with lesions

Foetal age: 6.2 ± 1.3 mo
- Normocholesterolemia
- Transient Hypercholesterolemia
- Hypercholesterolemia

Napoli et al. JCI 100, 2680, 1997
Pathways of Placental Lipid Metabolism

Maternal circulation

PLACENTA

Fetal circulation

Endocytic pathway
LDL receptor

Selective pathway

SR-BI

LDL

ACAT

CE

A-I

HDL
LDL and HDL receptor are expressed on the syncytiotrophoblast

Malassine et al. Histochem 1987

Wadsack & Desoye, unpublished
Pathways of Placental Lipid Metabolism

Maternal circulation

Endocytic pathway
LDL receptor

Selective pathway

Fetal circulation

Storage in Lipid Droplets

PLACENTA
Pathways of Placental Lipid Metabolism

Maternal circulation

PLACENTA

Fetal circulation

Endocytic pathway
LDL receptor

Selective pathway
SR-BI

Storage in Lipid Droplets

Steroid synthesis

Secretion to fetus

A-I
HDL

A-I
HDL

LDL

ACAT

CE

TG

PL

PLACENTA

Pathways of Placental Lipid Metabolism
Cholesterol efflux from placental endothelial cells to the foetal circulation

Circ Res. 104: 600, 2009
Phospholipid transfer protein (PLTP)

- Mediates PL transfer between lipoproteins  
  *(Huuskonen et al. Biochemistry 2000)*

- Involved in vitamin E delivery to endothelial cells  
  *(Desrumaux et al. FASEB J 1999)*

- Enhances cholesterol efflux to HDL  

- Contributes to the remodeling of HDL₃ → generation of large HDL₂ and nascent HDL particles  
PLTP modifies HDL
Placental PLTP is expressed foeto-placental endothelium and up-regulated in GDM

Insulin increases endothelial PLTP

PLTP modifies HDL to reduce atherogenic risk
Foetal glucose & insulin lead to multiple effects on metabolism at feto-placental interface

Foetal glucose & insulin lead to multiple effects on metabolism at feto-placental interface

compartment

maternal

stroma

fetal

syncytiotrophoblast

endothelium

↑ glucose

PLTP

↑

Adipocyte

PUFA

insulin

↑

HDL

3

HDL

2

ROS

Oxysterols

↑

Glucose uptake

↑

Metabolism

Liver

glucose

↑

↓

Metabolism

↑

Liver

↑

HDL3

preβHDL + HDL2
Insulin Upregulates Glycogen only in the Endothelium of Term Human Placenta

![Bar graph showing glycogen content in Trophoblast and Endothelium after 24 h treatment with insulin.]

- **Trophoblast**
  - Control
  - 1 nM insulin
  - 10 nM insulin

- **Endothelium**
  - Control
  - 1 nM insulin
  - 10 nM insulin

After 24 h treatment, glycogen content in the Endothelium increases significantly compared to control and 1 nM insulin treatment, with 10 nM insulin showing the highest increase. No significant difference is observed in the Trophoblast.

**Legend:**
- **PM**: Plasma Membrane
- **PM**: Phosphoinositide 3-Kinase (PI3K)
- **PI3K**: Phosphatidylinositol 3,4,5-trisphosphate (PIP3)
- **PDK 1/2**: Phosphoinositide-dependent protein kinase-1 (PDK)
- **GSK-3**: Glycogen synthase kinase 3 (GSK-3)
- **glycogen synthase**
- **glycogen**

**Result of fetal insulin:**
- Increase in glycogen synthase activity
- Decrease in GSK-3 activity

**IRS**?: Insulin Receptor Substrate?
Foetal glucose & insulin lead to multiple effects on metabolism at feto-placental interface.

- **Syncytiotrophoblast**
  - **Maternal**
  - **Endothelium**
  - **Fetal**
  - **Placental stroma**

**Compartments**

- **Glucose**
- **Insulin**
- **Oxysterols**
- **PLTP**
- **Glycogen**

**Metabolism**

- **Liver**
  - **Glucose uptake**
  - **Metabolism**

**Adipocyte**

- **PUFA**

**Signaling Pathways**

- **↑ glucose**
- **↓ ROS**
- **↑ Oxysterols**
- **↑ PLTP**
- **↑ insulin**
- **↑ HDL**
- **↑ preβHDL + HDL2**

The human placenta does not appear to limit maternal-to-foetal flux of glucose (and fatty acids)

The rate limiting step for maternal-to-foetal fatty acid transport is unknown

LCPUFAs are selectively transferred across placenta and extracted in foetus
The foetal glucose insulin axis is an important driver for maternal-foetal transport as well as for regulating foetal fat deposition.

The intrauterine environment of the first trimester of gestation may already play a key role in determining foetal growth.
Note of caution

- A-V difference
- Effect of foetal sex
- Third trimester/term of gestation vs earlier stages
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Thank you for your attention!