PLACENTAL TRANSFER OF FATTY ACIDS AND FETAL IMPLICATIONS

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FETAL PROGRAMMING

BRAIN

60% FAT (dry matter)

~ 40% LONG CHAIN POLYUNSATURATED FATTY ACIDS (LC-PUFA):

- 15% DOCOSAHEXAENOIC ACID (DHA, 22:6 n-3): Neuronal development

- 10% ARACHIDONIC ACID (AA, 20:4 n-6): Infantile Growth
Polyunsaturated FA Synthesis

**EFA:**
- 18:2\textbackslash 6, linoleic
- 18:3\textbackslash 6, \gamma\textbackslashed linolenic

**LC-PUFA:**
- 20:4\textbackslashed 6, arachidonic
- 20:5\textbackslashed 3, eicosapentaenoic
- 22:6\textbackslashed 3, docosahexaenoic

**Δ6-desaturase**
**Δ5-desaturase & elongase**

**PROSTA-GLANDINS**
**MEMBRANES**

**EFA and LC-PUFA PROVIDED BY PLACENTAL TRANSFER**
Fatty Acid Placental Uptake

Maternal circulation

LPL, Lipoprotein lipase
EL, Endothelial lipase

Facilitated Transport

Passive Diffusion

LPL, Lipoprotein lipase
EL, Endothelial lipase

PLA2 Lipases

FFA

FABPpm, FATP, FAT

LPL, Lipoprotein lipase
EL, Endothelial lipase

Trofoblast cytosol

membrane

Lipoprotein
R

PL

FFA
Placental transfer of fatty acids is a complex process that includes their binding to membrane and cytosolic protein carriers.

Fatty Acid Placental Transfer

- Placental transfer of fatty acids is a complex process that includes their binding to membrane and cytosolic protein carriers.

p-FABPpm (placental plasma fatty acid binding protein) not sequenced??.
## BIOMAGNIFICATION OF LC-PUFA

Fatty-Acid Percentages of Maternal and Cord Plasma Phospholipids

[median (IQR)]

<table>
<thead>
<tr>
<th></th>
<th>maternal</th>
<th>cord</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAT</strong></td>
<td>47.1 (2.5)</td>
<td>49.9 (1.7)</td>
</tr>
<tr>
<td><strong>MUFA</strong></td>
<td>14.9 (2.7)</td>
<td>13.4 (2.2)</td>
</tr>
<tr>
<td><strong>18:2n-6 (LA)</strong></td>
<td>21.0 (3.4)</td>
<td>7.4 (1.4)</td>
</tr>
<tr>
<td><strong>18:3n-3 (ALA)</strong></td>
<td>0.20 (0.10)</td>
<td>0.00 (0.03)</td>
</tr>
<tr>
<td><strong>20:4n-6 (AA)</strong></td>
<td>7.7 (1.9)</td>
<td>16.1 (2.5)</td>
</tr>
<tr>
<td><strong>22:6n-3 (DHA)</strong></td>
<td>2.9 (1.0)</td>
<td>4.8 (1.7)</td>
</tr>
</tbody>
</table>

Stable Isotope Study on FA Placental Transfer

PERILIP PROJECT (FP6 EU)

Aim

In vivo evaluation of the placental transfer of fatty acids labeled with stable isotopes in humans

Material and methods

Single oral dose of stable isotope tracer in a sugar cube:
- $^{13}$C-PA (Palmitic acid: saturated FA): 0.5 mg/Kg
- $^{13}$C-OA (Oleic acid: monounsaturated FA): 0.5 mg/Kg
- $^{13}$C-LA (Linoleic acid: essential FA): 0.5 mg/kg
- $^{13}$C-DHA (Docosahexaenoic acid, LC-PUFA): 0.1 mg/kg

- Study 4 hours before cesarean section (n=4)
- Study 12 hours before cesarean section (n=11)
4h FA Tracer Study

Appearance of $^{13}$C-FA enrichment in maternal plasma

Maternal Plasma TG

Maternal Plasma FFA

Maternal Plasma PL

No enrichment in Maternal Cholesterol Esters

N=4

4h FA Tracer Study

Distribution of tracer between placenta and plasma (M ± SEM)


\[
\text{(% Ratio placenta/plasma)} = \frac{\text{fatty acid concentration in placenta (µmol/g)} \times \text{APE-placenta}}{\text{fatty acid concentration in plasma (µmol/ml)} \times \text{APE-plasma}} \times 100
\]
Design of 12h FA tracer Study

Subjects: 11 pregnant women, elective caesarian section

- weight: 78 ± 8 kg
- height: 161 ± 6 cm
- age: 33 ± 4 years
- gestation: 39.8 ± 1 wk

Tracer administration (12h before caesarean section)

Oral application of stable isotope tracer in a sugar cube:

- palmitic acid ($^{13}$C-PA): 0.5 mg/kg
- oleic acid ($^{13}$C-OA): 0.5 mg/kg
- linoleic acid ($^{13}$C-LA): 0.5 mg/kg
- docosahexaenoic acid ($^{13}$C-DHA): 0.1 mg/kg

- Maternal blood: 0h, 9h, 10,11h, 12h (c-section), 13h
- Placenta collection and venous cord blood

$^{13}$C-enrichment of FA by gas chromatography combustion isotope ratio mass spectrometry (GC-C-IRMS)
13C-FA CONCENTRATION IN MATERNAL PLASMA

SATURATED FA

MONOUNSATURATED FA

ESSENTIAL FA

LC-PUFA

13C-PA (µmol/l)

13C-OA (µmol/l)

13C-LA (µmol/l)

13C-DHA (µmol/l)

P < 0.05
13C-FA enrichment in placental TG and NEFA tended to be high

Phospholipids constituted about 80-90% of FA in placenta

Mean ± SD, P < 0.05
12h FA tracer study

Distribution placenta/maternal plasma (M ± SEM)


Placenta

Comparison 4h vs 12h

Different letters: P<0.05

α = slope

* P<0.05
Distribution Cord/Maternal Plasma

\[
\text{(% Ratio) Cord/plasma AUC} = \frac{\text{FA concentration in cord (µmol/g) \times APE-cord plasma}}{\text{AUC FA concentration in plasma (µmol/ml) \times APE-mat. plasma}} \times 100
\]

Mean ± SD, \( P < 0.05 \)
PROYECTO NUHEAL: Placental PL

- Supplementation of 136 Spanish pregnant women from wk 20 to delivery

No significant changes in placental mRNA expression of FATP-1, FATP-4, FATP-6, FAT, FABPpm, H-FABP, B-FABP, A-FABP among the groups
DHA (%) IN MATERNAL PLASMA PL CORRELATES WITH PLACENTAL PROTEINS FATP-1 ($r=0.32$, $p=0.001$) AND FATP-4 ($r=0.23$, $p=0.012$)
NUHEAL: Correlations placental FA carriers-Cord Plasma PL


$r = +0.20; P = 0.032^*$
GESTATIONAL DIABETES MELLITUS

Normal plasma LC-PUFA in women with gestational diabetes mellitus, but low erythrocyte PL LC-PUFA in their babies (Wijendran et al. 2000)

Delayed brain maturity in these newborns compared to controls?

Pregestational or gestational diabetes mellitus was found to adversely affect attention span and motor functions of offspring at school age (Ornoy et al. 2001)
PRELIMINARY RESULTS

**GLUCOSE**

Maternal

<table>
<thead>
<tr>
<th>Maternal Control (n=22)</th>
<th>Maternal Gestational Diabetes (n=26)</th>
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**LC-PUFA n-3**

Maternal

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Control (n=22)

Gestational Diabetes (n=26)
PRELIMINARY RESULTS

VENOUS CORD BLOOD

SATURATED (SFA) EFA, LC-PUFA n-3

PLACENTAL TRANSFER OF LABELED FA IN GESTATIONAL DIABETES ON GOING

DHA P = 0.062
NEURONAL DEVELOPMENT IN BABIES FROM GESTATIONAL DIABETES MOTHERS DURING THE 1º YEAR OF LIFE

- Bayleys test (6 months and 12 months)
- Sleep/wake cycles by actigraphy methods
- Evaluation of circadian rhythms of temperature using temperature sensors.
Temperature sensor

Actimeter

Ondas medias de temperatura de la piel

Temperatura (°C)

Hora del día (hh:mm)

15 días

30 días

90 días
Different letters indicate significant differences by repeated measures ANOVA (for 15 days, 30 days and 3 months comparisons). Different numbers indicate significant differences when comparing babies (3 months) with child and adult groups.

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THANK YOU!