Placental Lipids and Fatty Acid Transfer in Maternal Overnutrition

Gernot Desoye
Dept Obstetrics and Gynaecology
Medical University of Graz, Graz Austria

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Fetal Phenotype in Diabesity

<table>
<thead>
<tr>
<th>Normal (10-90th centile)</th>
<th>Obese (&gt; 90th centile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.6 ± 5.7</td>
<td>32.2 ± 6.1 p&lt;0.001</td>
</tr>
</tbody>
</table>
Among Mammals

Human Newborns Have Highest % Body Fat

Kuzawa CW. Yearbook Physical Anthropol 41:177-209, 1998

0
data labels

Hamster
Rat
Pig
Caribou
Cat
Rabbit
Elephant seal
Mouse
Black bear
Foal
Calf
Lamb
Baboon
Sea lions
Fur seal
Harp seal
Guinea pig

% Body fat at birth

0
2
4
6
8
10
12
14
16
syncytiotrophoblast endothelium

fetal maternal

P L A C E N T A

Glucose

Lipogenesis

TG

Liver

FFA

HDL TG

Insulin ↑

Pedersen – Freinkel Concept Expanded
Pedersen – Freinkel Concept Expanded
Lipid Droplets

Free fatty acid

Dissociation

Lipoprotein Receptor

1-3% FA Albumin Complex

Hydrolysis by Lipases

97-99% FA Lipoproteins

EL
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

[Bar chart showing EL mRNA expression across different groups: lean, obese, lean GDM, and obese GDM.]

[Graph showing EL mRNA expression fold change compared to control for TNF-α and Leptin, with asterisks indicating statistical significance.]
Fatty Acid Transfer Across Term Human Placenta

Transfer characteristics:

• Slow (3% clearance of H\textsubscript{2}O)  
  \textit{Placenta 18: 635, 1997}

• Inefficient

• Dependent on chain length

• Maternal FAs contribute to only ~ 70g (20%) of neonatal fat (normal pregnancy)  
  \textit{Pediatr Res 7:192, 1973}

\textit{In vivo stable isotopes}

\begin{itemize}
\item[\textcolor{red}{13C-PA}] (16:0)  
\item[\textcolor{red}{13C-OA}] (18:1)  
\item[\textcolor{red}{13C-LA}] (18:2)  
\item[\textcolor{red}{13C-DHA}] (22:6)
\end{itemize}

\textcolor{red}{Normal}  
\textcolor{gray}{GDM}

\textit{Pagán A et al, AJP-Endocr Metab 2013}
Computer Model Predicts Transfer

Lewis R et al, Southampton, UK
Two Placental Fatty Acid Pools

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

Lewis R et al

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

How does the placenta handle the fatty acid excess of GDM & obesity?
Cleveland Cohort with Various Degrees of Obesity

<table>
<thead>
<tr>
<th>BMI</th>
<th>Number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean: 20-24.9</td>
<td>20</td>
</tr>
<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>
<td>20</td>
</tr>
</tbody>
</table>

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

Hirschmugl B et al, Int J Obes, in press
In Maternal Obesity the Human Placenta Stores More Triglycerides


Hirschmugl B et al, Int J Obes, in press
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

Hirschmugl B et al, Int J Obes, in press
Maternal BMI and Insulin Associate with Placental CGI-58

BMI vs CGI58 protein
R = 0.638
P < 0.001

BMI vs CGI58 RNA
R = 0.326
P = 0.005

Insulin vs CGI58 protein
R = 0.632
P < 0.001

Insulin vs CGI58 RNA
R = 0.204
P = 0.090

Hirschmugl B et al, Int J Obes, in press
Summary

Obesity

Syncytiotrophoblast

In the context of obesity, the diagram illustrates the involvement of FATP1 and FATP3 in lipid droplet formation and the enzymes PLIN2, PLIN3, ATGL, and CGI-58 in triglyceride (TG) metabolism. INSulin and IR signaling contribute to increased TG levels and lipid droplet formation. The conversion of triglycerides into DAG (diacylglycerol) and FA (fatty acids) is depicted, highlighting the pathways involved in early nutrition and development.
**maternal obesity**

Lipids/Fatty acids → Metabolism transfer → Fatty acids

Mother → Placenta → Foetus

Lipid Droplets

Free fatty acids

Fetal adiposity
Summary and Conclusion

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

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
Collaborators

*University of Southampton, UK*
Rohan Lewis
Simone Perazzolo
Bram Senger
Keith Godfrey
Sarah Crozier

*University of Murcia, ES*
Antonio Gázquez García
Elvira Larque

*University of Granada, ES*
Cristina Campos
Maite Segura

*University of Cleveland, OH, USA*
Pat Catalano
Sylvie Hauguel De Mouzon

*King's College London, UK*
Lucilla Poston
The Team

Christian Wadsack

Eva Kitzinger

Birgit Hirschmugl
Thank you for your attention!