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Paediatric Endocrinology
University of Auckland

The Fetal Footprint - Is There a Link between Fetal and Adult Health - Main Session
(Workshop options scheduled)
Sunday, 23 June 2013
Start 9:45am
Duration: 25mins
Baytrust
The fetal footprint: Is there a link between fetal and adult health

Wayne Cutfield
2013
Declaration

Pfizer sponsored speaker
Nutrition and health common misperception

Your health depends entirely on your lifestyle and your genes
Human Genome Project
Failed promise?

Common variations in genes account for <10% of common diseases such as obesity, diabetes, heart disease, and cancer.
Determinants of adult disease

- Genes
- Early life events
- Lifestyle
- Disease
As birth weight falls type 2 diabetes risk increases

<table>
<thead>
<tr>
<th>B Wt (gm) ratio</th>
<th>N</th>
<th>%</th>
<th>Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2500 SGA</td>
<td>20</td>
<td>30</td>
<td>6.6</td>
</tr>
<tr>
<td>-2900</td>
<td>54</td>
<td>19</td>
<td>4.8</td>
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<tr>
<td>-3400</td>
<td>114</td>
<td>17</td>
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<td>123</td>
<td>12</td>
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<td>64</td>
<td>6</td>
<td>1.4</td>
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<tr>
<td>&gt;4300</td>
<td>32</td>
<td>6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Fetal Origins (The Barker) Hypothesis

The origins of adult disease begin in utero. Fetal malnutrition is proposed as the cause of small birth size and programmed later adult disease.

Birth Weight and Type 2 Diabetes Risk in Twins

Lifespan Twin study (Sweden)
2,888 monozygotic adult twins
185 with type 2 DM

Odds Ratio of 1 kg decrease in birth weight and type 2 diabetes

Between twin pairs 2.23
Within twin pairs 2.03

Iliadou et al. Intl J Epidemiol 2004; 33: 948-53
Maternal famine affects the health of offspring

1\textsuperscript{st} trimester famine:
- Heart disease
- Lipid problems
- Obesity

2\textsuperscript{nd} trimester famine:
- Chronic lung disease

3\textsuperscript{rd} trimester famine:
- Diabetes risk

Painter R et al Reprod Tox 2005; 20: 345-52
Programming Sensitivity

Conception

1st Trimester  2nd Trimester  3rd Trimester

Sensitivity to programming

SGA 1-3%

Malnutrition

Overnutrition

LIGGINS INSTITUTE
THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Small at birth (SGA) children are insulin resistant.
Long Term Risks of Insulin Resistance

N=208 healthy adults
FU at 4-11 yr
Insulin suppression test
Birth Weight, BMI and Insulin Sensitivity

Ong et al. Diabetologia 2004; 47: 1064-70
Metabolic Changes in SGA Children

Fasting lipids:
- Increasing cholesterol in late childhood
- Dyslipidemia beginning to occur in young adulthood.

Blood pressure:
- Small increase in daytime systolic BP
- ↓ in normal night-time BP dipping (ABPM)
Programming Sensitivity

Sensitivity to programming

Conception

1st Trimester  2nd Trimester  3rd Trimester

SGA 1-3%

Prems 3-5%

Malnutrition

Overnutrition

Liggins Institute
The University of Auckland
New Zealand
Insulin Sensitivity

$S_i(10^{-4}\text{ min}^{-1}\text{ }\mu\text{U/ml})$

$<32\text{ wk gestation}$

Hofman et al. J Clin Endocrinol Metab 1997; 82; 402-6
Early Nutrition in Auckland VLBW infants

Low protein intake 0-4, 4-8, 8-12 wks
High lipid intake 4-8, 8-12 wks
High carbohydrate intake 4-8, 8-12 wks

Higher carbohydrate intake in the first month of life was associated with greater current BMI SDS (p<0.05).

Prematurely born adults are insulin resistant and overweight

Mathai S et al Diabetes 2012; 61: 2479-83
Prematurity and adult male adiposity

Mathai S et al Diabetes 2012; 61: 2479-83
Prematurity affects the next generation!

Children

Parents

Prematurity affects the next generation!

Mathai S et al Diabetes 2012; 61: 2479-83
Programming Sensitivity

Sensitivity to programming

Conception

1st Trimester

2nd Trimester

3rd Trimester

Post Term
2-4%

Prems
3-5%

SGA 1-3%

Overnutrition

Malnutrition

Liggins Institute
The University of Auckland
New Zealand
Background

Post-term children: born after 42 weeks of gestation

Incidence of post-terms highly variable: 0.4 – 12%

In Auckland 2009-10:
1.8% European, 2.5% Maori and PI
Post term children at 16 yrs

** p<0.01  *p<0.05

Females
• Same weight, height and BMI

Males
• Same height but higher weight
• Greater BMI
• 8/17 obese


N = 396
Insulin sensitivity

$Si = \frac{((\text{mU/L})\times\text{min})^{-1}}{\text{Adjusted for age and DEXA fat mass}}$

Ayyavoo A et al. PLoS One in press
Post term children

- Lower insulin sensitivity
- Higher cholesterol
- Greater abdominal fat
- Reduced nocturnal BP dipping
- At risk of the Metabolic Syndrome (diabetes, high blood pressure, greater abdominal fat and high lipids)
Programming Sensitivity

First born children 60%

Conception

1st Trimester 2nd Trimester 3rd Trimester

Sensitivity to programming

Post Term 2-4%

Prems 3-5%

SGA 1-3%

Malnutrition

Overnutrition

First born children 60%
Height

(1st vs 2nd vs 3rd borns)

Savage T et al Clin Endocrinol 2013; Jan 24 epub
IGF-I

First borns

Later borns

IGF-I (ng/ml)

p = 0.0002

Savage T et al Clin Endocrinol 2013; Jan 24 epub
First born children are different to later born children

1st borns 250 gm lighter
adjusted for

Acute insulin response (mU/l)

p = 0.019

First born children are different to later born children

First-born children are more likely to get diabetes... but they are taller and slimmer too

- First-born children found to have greater difficulty in absorbing sugars into the body
- Physical changes in the mother’s womb during her first pregnancy may help nutrient flow to future children

By CLAIRE BATES
PUBLISHED: 17:18 GMT, 13 February 2012 | UPDATED: 17:18 GMT, 13 February 2012

Being the eldest child has many advantages, such as having your parents full attention and avoiding cast-off clothes.
Conclusions

First borns are taller, insulin resistant with higher blood pressure.

We speculate that reduce placental vascularisation in first pregnancies leads to nutritional compromise and adverse metabolic programming.
Programming Sensitivity

First born children 60%

Hyperemesis 2%

Twins 2%

Older maternal age/older paternal age

IVF 2-4%

Post Term 2-4%

Prems 3-5%

SGA 1-3%

Sensitivity to programming

Conception

1st Trimester

2nd Trimester

3rd Trimester

Malnutrition

Overnutrition

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12th most viewed PLoS ONE article of all time (61,000+)

Increasing Maternal Age Is Associated with Taller Stature and Reduced Abdominal Fat in Their Children

Tim Savage, José G. B. Derraik, Harriet L. Miles, Fran Mouat, Paul L. Hofman, Wayne S. Cutfield

Metrics

- Views: 108,060
- Academic Bookmarks: 2
- Social Shares: 1,713

Comments

Reddit thread
Posted by MattUHodgkinson

Social conditions may still be at play
Posted by ric_ataide

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And the most viewed article...

Fellatio by Fruit Bats Prolongs Copulation Time

Min Tan, Gareth Jones, Guangjian Zhu, Jianping Ye, Tiyu Hong, Shanyi Zhou, Shuyi Zhang, Libiao Zhang

286,050 views
Programming Sensitivity

**First born children** 60%

**Hyperemesis** 2%

**Twins** 2%

**Older maternal age/older paternal age**

**IVF** 2-4%

**Post Term** 2-4%

**Prems** 3-5%

**SGA** 1-3%

**Maternal/fetal obesity** 27% / **maternal gest. Diabetes** 4-15%

**Conception**

1st Trimester 2nd Trimester 3rd Trimester

Sensitivity to programming

Overnutrition

Malnutrition

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Birth Weight and Type 2 Diabetes Risk in Taiwanese Children

Wei et al Diabetes Care 2003; 26: 343-8
Gestational diabetes leads to offspring obesity

Mothers with glucose screening in pregnancy

9,439 offspring

GCT: 1 hr 50 gm glucose challenge test

Hillier TA et al Diab Care 2007; 30: 2287-92
Conclusions

The optimal fetal environment is delicately poised.

Deviation away from average progressively increases risks of obesity, diabetes and cardiovascular disease.
Conclusions

Nutrition prior to and during pregnancy affects the health of offspring lifelong.

Excessive weight gain following fetal undernutrition or malnutrition amplifies programmed risks of metabolic disease.
Conclusions

What more to do

The triggers and mechanisms of developmental programming remain elusive and unclear.

The contribution of early life events to adult metabolic disease need to be more accurately quantified.
Acknowledgements

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Ahila Ayyavoo
Ben Albert
Janene Biggs
Christine Brennan
William Schierding
Long term diabetes risk of insulin resistance

2 hr glucose values in 702 50 yr old adults exposed to famine in utero

p value for famine 0.0009
Low birth weight and metabolic syndrome

PREMA study
1,270 children followed to adolescence

Efstathiou SP et al Circul 2012; 125: 902-10
Body Composition in SGA Children

29 SGA, 22 AGA. No differences in Ht, Wt nor BMI at 2, 3, or 4 yrs

Ibanez et al. J Clin Endocrinol Metab 2006; 91: 2153-8
Speculation

Double hit phenomenon:

Common gene variant leads to prolonged gestation and risk of metabolic syndrome

The nutritional and physiological stress of prolonged gestation amplifies metabolic syndrome risks