Glycemic Load in Pregnancy

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Maternal Obesity

Glucose, insulin, leptin, lipids, inflammatory response

Fetal macrosomia. Persistently altered energy balance

Childhood and Adulthood Obesity

Transgenerational ‘Acceleration ‘ of Obesity?
High birth weight and obesity—a vicious circle across generations. (Cnattingius S et al 2011)

- 162 676 mothers and first born offspring Swedish Birth Register 1973-2006

- Mothers born large for gestational age (LGA) had increased risk of overweight, obesity Class I, II and III

- Risk of LGA delivery increased with mother’s BMI

- Risk of LGA highest in women with high BMI and LGA themselves

- Conclusion. Prevention of LGA births may curb the intergenerational vicious cycle of obesity
Glucose homeostasis in pregnancy

- Insulin resistance increases with gestation in normal pregnancy
- Leads to maternal plasma glucose
  - Fetal insulin
  - Fetal growth

Exacerbated in:
- gestational diabetes mellitus
- obese pregnancies
Association between Maternal Fasting Plasma Glucose and % LGA deliveries (Metzger et al, NEJM 2008). HAPO study
Association between Maternal Fasting Plasma Glucose and Neonatal Fat >90\textsuperscript{th} centile (Metzger et al, Diabetes Care, 2009)

HAPO study

\% > 90\textsuperscript{th} centile fat mass

Maternal fasting glucose
Post-prandial Glucose associated with fetal growth (Parretti et al, 2001)

- Pregnant women; studied every two weeks between 28 and 38 weeks’ gestation
- Blood glucose levels recorded post prandially every two hr
- Ultrasound scans 22, 28, 32 and 36 weeks
- Significant association between post prandial glucose 1hr and measures of fetal adiposity
Blood Glucose profile in Obese Pregnant Women in Early and Late Pregnancy (non-diabetic)

Harmon KA et al, Diabetes Care 2011

PPB –post prandial breakfast; PPL-post prandial lunch; Pre-E; pre-dinner; PPD post prandial dinner
Relationships between maternal variables in obese pregnancies and infant fat mass

**A**

\[ \text{BFat} \% = 0.095 \times \text{Glucose} - 1.535 \]

\[ r = 0.48 \]
\[ p = 0.02 \]

**B**

\[ \text{BFat} \% = 0.122 \times \text{INSULIN} + 7.08 \]

\[ r = 0.49 \]
\[ p = 0.01 \]

**C**

\[ \text{BFat} \% = 0.006 \times \text{FFA} + 6.26 \]

\[ r = 0.54 \]
\[ p = 0.004 \]

**D**

\[ \text{BFat} \% = 0.022 \times \text{TG} + 5.65 \]

\[ r = 0.67 \]
\[ p < 0.001 \]
Interventions to reduce plasma glucose and delivery of large for gestational age infants?
With anti-diabetic drugs?
Understanding the Glycemic Index (GI)

What is it?

- A way of ranking foods according to the effect they have on blood glucose concentration.

- Foods are ranked from 0 to 100 according to the extent they raise blood sugar levels after eating.
How GI is measured

- Foods that are rapidly digested and absorbed raise blood sugar quickly and are given high GI values.

- Foods that are digested and absorbed slowly raise blood sugar gradually and are given low GI values.
Effect of GI on blood sugar

A high GI food raises blood sugar levels quickly

A low GI food raises blood sugar levels slowly
Glycemic Index integrated area under the curve for blood sugar for a 50g load of available carbohydrate.

GLUCOSE (reference food)

Blood sugar levels

100%

1 hour 2 hours

SPAGHETTI (test food)

Blood sugar levels

41%

1 hour 2 hours
High/medium GI foods

White bread
Sugary soft drinks
Mashed potatoes

Refined breakfast cereals
Table sugar
White rice
Most fruit and vegetables

Diet soft drinks

Pasta

Low GI foods

Porridge

Nuts and raisins

Basmati rice
Factors Influencing GI Ranking

- Type of starch
- Cooking
- Physical structure
- Food processing
- Viscosity of fibre
- Type of sugar
- Acid content
- Fat content
- Protein content
Evidence supporting use of Low GI Diets

- Meta-analysis (Barclay et al, 2008)
  - Previous findings from observational studies inconsistent.
  - Systematic review of 37 prospective cohort studies
    - Low GI diet reduces T2DM
    - Low GI diet reduces CHD
  - Protection comparable to whole grain/ high fibre evidence.

“There is considerable evidence that a diet with an average GI of approximately 45 will achieve a significant reduction in the risk of chronic disease.”

(Barclay et al, 2008 & Brand-Miller et al. 2003)
Low GI Diets and Diabetes Control

Meta-analysis of 14 studies, 356 subjects (types 1 & 2 DM)

Mean difference
- glycated proteins were reduced by 7.4%
- 0.43% points in HbA1c reduction compared with high GI diet

(Brand-Miller et al, 2003)
Low GI and weight management

- Cochrane review (Thomas et al., 2007)
- Low glycaemic index or low glycaemic load diets for overweight and obesity - 6 RCT eligible
- Low GI versus conventional diet:
  - 1.1kg reduction in weight
  - 0.22 mmol/L reduction in total cholesterol
- No adverse effects reported in any study

“In studies comparing ad libitum low GI diets to conventional restricted energy low-fat diets, participants fared as well or better on the low GI diet, even though they could eat as much as desired”

(Thomas et al., 2007)
Glycemic Load (GL)

- Proposed as a more realistic tool to assess the glycemic response to foods.

- Takes into account carbohydrate content of food and portion size.

- Calculated as:
  - the amount of carbohydrate in a food (g) x its GI / 100

- Low GL = 10 or less
  - Medium GL = 11- 19
  - High GL = 20 or more
Intervention studies; low GI diet for Prevention of GDM – influence on fasting glucose and macrosomia

### A Outcome maternal fasting blood glucose

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>LGI Mean</th>
<th>SD</th>
<th>Total</th>
<th>HGI Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clapp 1997</td>
<td>3.78</td>
<td>0.348</td>
<td>10</td>
<td>4.25</td>
<td>0.696</td>
<td>10</td>
<td>12.2%</td>
<td>-0.47 [-0.95, 0.01]</td>
<td></td>
</tr>
<tr>
<td>Moses 2006</td>
<td>4.1</td>
<td>0.57</td>
<td>32</td>
<td>4.3</td>
<td>0.55</td>
<td>30</td>
<td>36.6%</td>
<td>-0.20 [-0.48, 0.08]</td>
<td></td>
</tr>
<tr>
<td>Rhodes 2010</td>
<td>-0.028</td>
<td>0.39</td>
<td>18</td>
<td>-0.028</td>
<td>0.29</td>
<td>14</td>
<td>51.2%</td>
<td>0.00 [-0.24, 0.24]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>60</td>
<td></td>
<td></td>
<td>54</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>-0.13 [-0.30, 0.04]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.32, df = 2 (p = 0.19); I² = 40%
Test for overall effect: Z = 1.52 (p = 0.13)

### B Outcome large-for-gestational age

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>LGI Events</th>
<th>Total</th>
<th>HGI Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clapp 1997</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>43.7%</td>
<td>0.05 [0.00, 0.72]</td>
<td></td>
</tr>
<tr>
<td>Moses 2006</td>
<td>1</td>
<td>32</td>
<td>10</td>
<td>30</td>
<td>43.0%</td>
<td>0.09 [0.01, 0.69]</td>
<td></td>
</tr>
<tr>
<td>Rhodes 2010</td>
<td>2</td>
<td>24</td>
<td>3</td>
<td>21</td>
<td>13.3%</td>
<td>0.58 [0.11, 3.16]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>66</strong></td>
<td></td>
<td><strong>61</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.14 [0.05, 0.41]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3
Heterogeneity: Chi² = 3.52, df = 2 (p = 0.17); I² = 43%
Test for overall effect: Z = 3.55 (p = 0.0004)

Oostdam et al, Journal of Women’s Health 2011
National trend in maternal obesity compared to general population

*General Population data Source, Health Survey for England 2006
(http://www.ic.nhs.uk/webfiles/publications/HSE06/ADULT%20TREND%20TABLES%202006.xls)

Obesity and Pregnancy Outcomes

Maternal risk
- Gestational diabetes
- Pre-eclampsia
- Venous thromboembolism
- Genital Infection
- Urinary tract infection
- Wound infection
- Postpartum haemorrhage
- Induction of labour

Fetal/infant risk
- Macrosomia
- Shoulder dystocia
- Brachial Plexus damage
- Intrauterine death
- Spina Bifida
- Heart defects
Work Package 11 (partners UGR, LMU Muenchen, Abbott)

An intervention of diet (low GI) and physical activity in obese pregnant women (n=1562; UPBEAT study KCL, recruitment ongoing 2010-2013)...

In the EarlyNutrition programme, 3 year old children of UPBEAT participants will be studied
The UPBEAT trial

Complex intervention of low GI diet and physical activity in 1562 obese women

–Pilot RCT- 110 women completed;
  ➢ does intervention lead to change in dietary and physical activity behaviour?
  ➢ barriers to behavioural change?
  ➢ acceptability

–Multicentre RCT
  Primary Outcome:
  ➢ Maternal: OGTT at 28weeks
  ➢ Neonatal: macrosomia

Secondary outcomes
  ➢ Neonatal, 6mth and 3 yr adiposity
The Rationale for Combining Physical Activity and Low Glycemic Index Diet Intervention in Obese Pregnancy

- Regular physical activity lowers insulin resistance in pregnancy (Clapp 2006)
- Physical activity improves control of GDM (Brankston et al, 2004)
- Physical activity prior to and in pregnancy reduces risk of GDM (Dempsey et al, 2004)
- Two trials; exercise training more effective than standard care in prevention of macrosomia (RR 0.36 95%CI0.13-0.99) (Barakat et al 2009; Hopkins et al 2010)
- Systemic review suggests reduction in macrosomia in non-diabetic women on low GI diet (Oostdam et al, 2011).
Recruitment BMI >30kg/m²

Randomisation 15-17 weeks’ gestation

All women

Baseline Physical Activity (PA), Diet

28 weeks’ gestation OGTT, PA, Diet

36 weeks’ gestation PA, Diet

Intervention arm

1:1 Health Trainer Interview
Handbook
Exercise DVD
8 weekly sessions
(SMART goals)
Diet 24-hour recall

‘Triple Pass’ method

1) Quick list

2) Detailed information (portion size & prompting)

3) Review

SPECIFIC FOOD DESCRIPTION PROMPT SHEET

<table>
<thead>
<tr>
<th>Food</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biscuits</td>
<td>Name and type Chocolate covered, iced, sandwich (cream, jam)</td>
</tr>
<tr>
<td>Bread</td>
<td>Name and type White, High fibre white, Brown, Brown with added bran, Granary, Wholemeal, Wheat Germ, Soda, French</td>
</tr>
<tr>
<td>Breakfast cereals (including porridge)</td>
<td>Name and type Added fruit and/or nuts? Muesli — added sugar/fruits? Porridge — made with oats or cornmeal? Instant? Made with milk or water or both? Type of milk on cereal/porridge.</td>
</tr>
<tr>
<td>Butter, margarine and spreads</td>
<td>Full product name/brand Butter? Spreadsable butter? Spreads - Is it polyunsaturated? Is it with olive oil? % fat if known (grams of fat per 100g)</td>
</tr>
<tr>
<td>Cakes</td>
<td>Type e.g. Sponge or fruit? If fruit: rich fruit cake? Flavour e.g. chocolate, icing, fresh cream, jam filling, butter cream filling?</td>
</tr>
<tr>
<td>Cheese</td>
<td>Name of product and type Standard/half fat/reduced fat</td>
</tr>
<tr>
<td>Chocolates</td>
<td>Type e.g. milk, plain, white Any filling and, if so, what type e.g. water, caramel etc? Any additions e.g. raisins, nuts etc?</td>
</tr>
<tr>
<td>Chips</td>
<td>If made at home: frozen, oven, microwave, fresh cut. If take-away, where from i.e. fish &amp; chip shop, Chinese, McDonalds Cut: thick/thin/ crinkle/French fries</td>
</tr>
<tr>
<td>Cream</td>
<td>Single, double, whipping, aerosol Imitation cream e.g. Emiez Coconut cream — normal or reduced fat?</td>
</tr>
<tr>
<td>Crisps</td>
<td>Name of product and type Standard/low fat/low salt Potato, corn, wheat, maize, vegetable, plantain etc Flavour Prompt: from a multipack?</td>
</tr>
<tr>
<td>Fruit, vegetables, pulses - canned</td>
<td>Name and type Fruit - canned in water/sweetened juice/syrup Vegetables/pulses - standard, reduced sugar, reduced salt or both e.g. reduced sugar and salt baked beans</td>
</tr>
<tr>
<td>Meat</td>
<td>Type of meat (name of animal, cut of meat, preparation e.g. minced) Standard or lean e.g. very lean mince beef</td>
</tr>
</tbody>
</table>
## Pilot Study Results; Glycaemic Load

### Triple pass 24hr recall before and after intervention

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong>*</td>
<td>n=59, 50</td>
<td>n=58, 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Energy intake (kcal)</td>
<td>Baseline</td>
<td>1875 (569)</td>
<td>1753 (553)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 weeks</td>
<td>1864 (564)</td>
<td>1646 (690)</td>
<td>-189 (-434 to 56)</td>
</tr>
<tr>
<td>Global GI</td>
<td>Baseline</td>
<td>57.6 (6.2)</td>
<td>58.3 (5.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 weeks</td>
<td>67.8 (36.3)</td>
<td>52.4 (13.2)</td>
<td>-15.5 (-26.4 to -4.6)</td>
</tr>
<tr>
<td>Dietary GL</td>
<td>Baseline</td>
<td>137(50)</td>
<td>128 (43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 weeks</td>
<td>150 (58)</td>
<td>110 (42)</td>
<td>-34 (-51 to -17)</td>
</tr>
</tbody>
</table>

Global GI; GL/ carbohydrate intake
Primary endpoint:
Infant large for gestational age
Birthweight >90th centile
Target 25% reduction (14.4 to 10.8%)
N= 2,832
ROLO Study  
(Dublin, Ireland)

Hypothesis.

Alteration of the source of maternal dietary carbohydrate would prove valuable in the prevention of fetal macrosomia in at risk women (with previous LGA delivery)
Intervention arm:

- Single dietary education session
- Small groups of 2 – 6 people
- Lasted 2 hours
- Gestation 15.7+/−3.0 weeks
Dietary Intervention

- Women were first given advice on healthy eating guidelines for pregnancy
- Focused on the glycemic index
- No advice on gestational weight
## Results – GI Index

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group Low GI diet</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pregnancy</td>
<td>57.3 ± 4.2</td>
<td>57.7 ± 4.0</td>
</tr>
<tr>
<td>Second trimester</td>
<td>56.1 ± 4.0</td>
<td>57.8 ± 3.7 *</td>
</tr>
<tr>
<td>Third trimester</td>
<td>56.0 ± 3.8</td>
<td>57.7 ± 3.9 *</td>
</tr>
</tbody>
</table>
## Results - Compliance

<table>
<thead>
<tr>
<th>Compliance Scale</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed the diet ‘all of the time’</td>
<td>3.8</td>
</tr>
<tr>
<td>Followed the diet ‘most of the time’</td>
<td>76.4</td>
</tr>
<tr>
<td>Followed the diet ‘some of the time’</td>
<td>17.0</td>
</tr>
<tr>
<td>Followed the diet ‘none of the time’</td>
<td>2.8</td>
</tr>
</tbody>
</table>
A new trial in 720 obese pregnant women randomised to a low GI dietary substitute form 16-18 week’s gestation until delivery (partner Abbott) or to standard care.

Primary outcome; neonatal fat mass

PILOT STUDY about to start
Aim of Pilot study

- To evaluate relative efficacy of 3 low GI supplements versus a control on post-test glycemic response; capillary blood glucose sampling

- With the most promising supplement, evaluate effect on post prandial glycemic response; Continuous glucose monitoring
Continuous Glucose Monitoring Sensors
Abbott FreeStyle® Navigator

- Subcutaneous electrochemical enzymatic sensor inserted under the skin to a depth of ~5mm
- Connect via blue-tooth technology to receiver
- Measures glucose concentration of interstitial fluid
- Lag time: physiological delay 10-15 min between change in blood & interstitial glucose
- In-built glucometer
- Can be worn for 5 days
The prototype with the most superior glucose lowering effect demonstrated in stage 1 will be taken to stage 2.

A CHO and calorie controlled diet will be provided for the 48hr period following ingestion of the control/prototype.

15 min interval venous sampling will be performed up to 210min following ingestion of prototype or control.

CGMS will be inserted to assess longer impact of the low GI supplement v control over 48 hrs.

Sample analysis; glucose, insulin, c-peptide, TAG and NEFA.
The UPBEAT team
Annette Briley
Rahat Maitland
Suzanne Barr

Ricardo Rueda
Barbara Marriage
Fiona McAuliffe and ROLO team
Thank you for your attention!
Postprandial maternal hyperglycemia in sheep leads to increased fetal growth (Smith et al, BJOG 2009)

Fetal birthweight (p=0.032) and fetal glucose (p<0.001) increased in sheep exposed to maternal post prandial hyperglycaemia induced by propylene glycol.