Developmental origins of Type 2 diabetes and obesity - Maternal obesity, GDM and the NCD Epidemic

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Dept of Medicine & Therapeutics
Chinese University of Hong Kong
Outline

• Epidemiology of Diabetes and Obesity in Asia
• Risk factors for Diabetes
• Role of the intra-uterine environment
• Gestational Diabetes and long-term risks
• Implications for strategies to prevent diabetes and obesity
Diabetes In Asia

Ramachandran A, Ma RC and Snehalatha DC, Lancet 2010; Jan 30; 375: 408-18
Epidemiology of Diabetes in Hong Kong

- T2 DM affecting 10% of population (in 1990s)
- 10-30% have MetS
- 97% type 2 DM
- Affects 1 in 4 aged > 65
- Among aged 25-34, 2% have DM
- Around 20% of DM patients are aged < 40
  - Risk of CHD ↑14x
  - Risk of CVA ↑30x
  - Nephropathy
Type 2 diabetes as a Progressive Disease

-10
Prevention

0
Diagnosis

10+
Years

IFG/IGT

Type 2 diabetes

β-cell function

Insulin resistance

Blood glucose

Macrovascular complications

Microvascular complications

IFG: impaired fasting glucose
IGT: impaired glucose tolerance

Adapted from DeFronzo RA. Med Clin N Am 2004;88:787–835.
Disparity between prevalence of diabetes and obesity in Asia

Young onset, strong FH, central obesity  
Yoon et al, Lancet 2006
Ramachandran, Ma et al. Lancet 2010
Relationship between BMI and DM prevalence

Adapted from Nyamdorj et al, Int J Obes 2010

DECODA Study Group

Adapted from Nyamdorj et al, Int J Obes 2010
Evidence supporting role of intra-uterine environment in DM

• 1) Link between birthweight and DM
• 2) Maternal nutrition and risk of DM
• 3) Transgenerational effects
• 4) Increased maternal transmission of DM
• 5) Animal models of in-utero malnutrition or overnutrition
Early Epidemiological links:
The Hertfordshire Cohort

15726 people born
1911-1930

Low birthweight asso. with:
Increased mortality from CHD
Increased risk of T2 DM, IGT

**Birthweight and Type 2 DM risk**

**OR 0.75 (0.70-0.81) for T2 DM per 1kg increase in Bwt**

Whincup P et al, JAMA 2008
Exposure to Chinese famine and hyperglycaemia in adults

7,874 rural adults
From China
National Nutrition and Health survey
Examined exposure to Chinese famine 1959-61

Risk of hyperglycaemia
OR 3.92

Li Y et al, Diabetes 2010
Transgenerational diabetes

• Early epidemiological studies in the Pima Indian population revealed increased risk of diabetes in offspring of mothers with diabetes (Pettit et al, Diabetes 1988)

• Excess in maternal transmission has been observed in all races and both sexes in a multiethnic cohort (Karter et al, Diabetes Care 1999)

• Risk of DM higher among sibs exposed to intrauterine hyperglycaemia. Sibs exposed to in-utero DM had higher BMI (Dabelea et al, Diabetes 2000), and younger onset of DM (Pettit et al, Diabetes Care 2008)

• Increased risk of DM also seen in offspring of T1 DM (Sobnogwi et al, Lancet 2003)
Among 2310 Chinese patients with late-onset diabetes (onset >35yrs)

- 25% of subjects with DM have at least 1 diabetic parent, and irrespective of sex, were more likely to have a diabetic mother than a diabetic father
  - 17% vs 13% of male (p<0.01)
  - 18% vs 9% of female (p<0.01)

- Maternal influence and sex-specific parental effects

Lee SC et al, Diabetes Care 2000; 23: 1365-1368
Increased cardiometabolic risk in offspring exposed to GDM at 8yrs

<table>
<thead>
<tr>
<th>Maternal Characteristics at Pregnancy</th>
<th>NGT (N=101)</th>
<th>GDM (N=63)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at delivery (years)</td>
<td>28.0</td>
<td>28.5</td>
<td>0.064</td>
</tr>
<tr>
<td>% Caesarean delivery</td>
<td>9.9</td>
<td>33.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% male infants</td>
<td>54.5</td>
<td>41.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Birth weight of infant (gram)</td>
<td>3245</td>
<td>3292</td>
<td>0.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children’s Characteristics at Follow-Up</th>
<th>NGT (N=101)</th>
<th>GDM (N=63)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>8.4</td>
<td>7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>28.2</td>
<td>28.1</td>
<td>0.92</td>
</tr>
<tr>
<td>Systolic BP (mmHg)*</td>
<td>88</td>
<td>94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)*</td>
<td>57</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)*</td>
<td>1.71</td>
<td>1.58</td>
<td>0.019</td>
</tr>
<tr>
<td>Mother with DM at FU</td>
<td>2</td>
<td>6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Tam WH, Ma RC et al, Paediatrics 2008
## Children’s long term risk after exposure to GDM- 15 year follow-up

<table>
<thead>
<tr>
<th>Hyperinsulinaemia</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 15 year FU</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>22.2% 2.7% 17.6</td>
</tr>
<tr>
<td>Overweight (BMI ≥ 90 percentile)</td>
<td>44.4% 13.7% 10.8</td>
</tr>
</tbody>
</table>

**Metabolic syndrome of children (≥ any 3)**
- WC ≥ age-sex specific 90th percentile
- FPG ≥5.6 mmol/L
- BP ≥ age-sex specific 90th percentile
- Fasting plasma triglyceride ≥1.7 mmol/L
- HDL-C <1.03 mmol/L

Tam WH, Ma RC et al. *Diabetes Care* 2010
Gradient between maternal glucose and adiposity

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>( &gt;90\text{th percentile} )</th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;4.2)</td>
<td>3,340</td>
<td>177 (5.3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>(4.2-4.4)</td>
<td>6,270</td>
<td>480 (7.7)</td>
<td>1.48 (1.24–1.77)</td>
<td>1.39 (1.16–1.66)</td>
</tr>
<tr>
<td>(4.5-4.7)</td>
<td>5,186</td>
<td>504 (9.7)</td>
<td>1.92 (1.61–2.30)</td>
<td>1.66 (1.38–1.99)</td>
</tr>
<tr>
<td>(4.8-4.9)</td>
<td>2,287</td>
<td>278 (12.2)</td>
<td>2.47 (2.03–3.01)</td>
<td>2.00 (1.64–2.45)</td>
</tr>
<tr>
<td>(5.0-5.2)</td>
<td>1,556</td>
<td>259 (16.6)</td>
<td>3.57 (2.92–4.37)</td>
<td>2.72 (2.20–3.36)</td>
</tr>
<tr>
<td>(5.3-5.5)</td>
<td>576</td>
<td>119 (20.7)</td>
<td>4.65 (3.62–5.99)</td>
<td>3.37 (2.59–4.38)</td>
</tr>
<tr>
<td>(\geq5.6)</td>
<td>174</td>
<td>46 (26.4)</td>
<td>6.42 (4.44–9.20)</td>
<td>4.71 (3.22–6.80)</td>
</tr>
<tr>
<td>Continuous(\dagger)</td>
<td>19,389</td>
<td>1,863 (9.6)</td>
<td>1.52 (1.45–1.59)</td>
<td>1.39 (1.33–1.47)</td>
</tr>
<tr>
<td><strong>1-h Plasma glucose (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq5.8)</td>
<td>3,482</td>
<td>212 (6.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>(5.9-7.3)</td>
<td>6,258</td>
<td>483 (7.7)</td>
<td>1.29 (1.09–1.52)</td>
<td>1.22 (1.03–1.45)</td>
</tr>
<tr>
<td>(7.4-8.6)</td>
<td>5,007</td>
<td>468 (9.3)</td>
<td>1.50 (1.34–1.88)</td>
<td>1.50 (1.26–1.78)</td>
</tr>
<tr>
<td>(8.7-9.5)</td>
<td>2,324</td>
<td>310 (13.3)</td>
<td>2.37 (1.98–2.85)</td>
<td>2.22 (1.84–2.69)</td>
</tr>
<tr>
<td>(9.6-10.7)</td>
<td>1,570</td>
<td>245 (15.6)</td>
<td>2.85 (2.35–3.46)</td>
<td>2.63 (2.14–3.22)</td>
</tr>
<tr>
<td>(10.8-11.7)</td>
<td>536</td>
<td>103 (19.2)</td>
<td>3.67 (2.84–4.74)</td>
<td>3.58 (2.59–4.41)</td>
</tr>
<tr>
<td>(\geq11.8)</td>
<td>212</td>
<td>42 (19.8)</td>
<td>3.81 (2.64–5.49)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq5.0)</td>
<td>3,537</td>
<td>209 (5.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>(5.1-6.0)</td>
<td>6,135</td>
<td>496 (8.1)</td>
<td>1.40 (1.18–1.66)</td>
<td>1.32 (1.11–1.56)</td>
</tr>
<tr>
<td>(6.1-6.9)</td>
<td>4,948</td>
<td>481 (9.7)</td>
<td>1.71 (1.45–2.03)</td>
<td>1.60 (1.35–1.90)</td>
</tr>
<tr>
<td>(7.0-7.7)</td>
<td>2,556</td>
<td>352 (13.8)</td>
<td>2.54 (2.13–3.04)</td>
<td>2.38 (1.98–2.86)</td>
</tr>
<tr>
<td>(7.8-8.7)</td>
<td>1,444</td>
<td>198 (13.7)</td>
<td>2.53 (2.06–3.11)</td>
<td>2.30 (1.93–2.95)</td>
</tr>
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<td>576</td>
<td>90 (15.6)</td>
<td>2.95 (2.26–3.84)</td>
<td>2.80 (2.13–3.69)</td>
</tr>
<tr>
<td>(\geq9.9)</td>
<td>193</td>
<td>37 (19.2)</td>
<td>3.78 (2.57–5.55)</td>
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<td>1.37 (1.31–1.44)</td>
<td>1.36 (1.30–1.43)</td>
</tr>
</tbody>
</table>

Around 200000 offspring

HAPO investigators, Diabetes 2009; 58: 453-459
Extending the Pederson Hypothesis to milder degrees of in-utero hyperglycaemia

Transgenerational diabetes

Barker
maternal undernutrition
('Marasmus-like')
small baby
fat wasted

Pederson
fetal overnutrition
('Kwashiorkor-like')
large baby
fat retention

Insulin resistance
Metabolic syndrome
Prediabetes
Diabetes

Hadden DR. Diabet Med 2008; 25: 1-10
Maternal Obesity and Hyperglycaemia interact to increase risk

<table>
<thead>
<tr>
<th>BMI</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>ORs for birth weight &gt;90th percentile: plasma glucose and BMI combined</td>
<td></td>
</tr>
<tr>
<td>Normal, underweight</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.75</td>
</tr>
<tr>
<td>Obese</td>
<td>2.07</td>
</tr>
<tr>
<td>Mean difference in birth weight: plasma glucose and BMI combined (g)</td>
<td></td>
</tr>
<tr>
<td>Normal, underweight</td>
<td>0</td>
</tr>
<tr>
<td>Overweight</td>
<td>124</td>
</tr>
<tr>
<td>Obese</td>
<td>174</td>
</tr>
</tbody>
</table>

*Adjusted for gestational age at delivery, ethnicity, baby’s sex, parity, maternal age, height and gestational age at the OGTT, smoking, alcohol use, hospitalization before delivery, family history of diabetes, and mean arterial pressure. All ORs and differences in birth weight compared with the referent group were significant (P < 0.001).
Contribution of maternal hyperglycaemia and obesity

• SEARCH case-control study
  – 79 youths with T2 DM
  – 190 normal youths
  – Overall, 47.2% of T2 DM in youth attributable to maternal DM or maternal obesity

Dabelea D et al, Diabetes Care 2008
Maternal factors

- Obesity
- Family History
- Genetics
- PCOS
- Low-grade infections

↑ Risk of GDM

In-utero over-nutrition

↑ Risk of DM in offspring

Offspring factors

- Physical inactivity
- Obesity
- Family History
- Genetics
- epigenetics
- Education
- Sleep deprivation

Ma RC and Chan JC. Int J Gynaec Obst 2009
Animal models of fetal programming of DM

• Rats, guinea pigs, mice, sheep, pigs etc.
• Maternal undernutrition
  – Protein undernutrition
  – Low calorie diet
  – Uterine artery ligation
  – IUGR
• Maternal overnutrition
  – High fat feeding
  – Maternal obesity
  – Maternal diabetes
Intra-uterine nutrition and adipocyte

Prenatal overnutrition

- ↑ PPARγ,
- ↑ leptin
- ↑ sc fat
- ↑ leptin
- Leptin resistance
- Weight gain
- Obesity

Reduced fetal nutrition

- Reduced adiposity
- ↓ leptin
- Low birthweight
- Rapid postnatal growth
- ↑ visceral fat
- ↑ PPAR γ
- ↑ Visceral fat mass
- Insulin resistance
- Type 2 DM

Muhlhausler et al, Trends Endocrinol Metab 2008
Diabetes Risk Begins In Utero

Woo M and Patti ME. Cell Metab 2008
Prenatal, perinatal and postnatal factors and Type 1 diabetes mellitus

- Perinatal and intrauterine factors:
  - Transplacental transmission of antibodies
  - Cesarean deliveries
  - Birthweight
  - Interplay between maternal age and birth order

- Prenatal factors:
  - Genetic factors
  - HLA genotype

- Islet autoimmunity

- Clinical type 1 diabetes mellitus

- Postnatal factors:
  - Breastfeeding
  - Cow’s milk exposure
  - Vitamin D intake
  - Childhood infections
  - Obesity
  - Viral infections
  - Other dietary factors

Ma, R. C. W. and Chan, J. C. N. (2009)
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2009.180
“Medicine might be winning the battle of glucose control, but is losing the war against diabetes.”

The Lancet, 26 June 2010
How the first nine months shape the rest of your life
The new science of fetal origins
By Annie Murphy Paul

“A Womb with a View”
-New York Times 27.9.10
Window of opportunity for Prevention of NCD

Hanson M et al, Prog Biophy Mol Biol 2011
Pre-pregnancy
• Education on the importance of good glycaemic control to optimize pregnancy outcome
• Screen for diabetes before conception in subjects with risk factors
• Encourage adequate physical activity
• Advocate balanced nutrition

During Pregnancy
• Early screening for pre-existing overt diabetes
• Repeat OGTT screening for GDM at 24-28 weeks if negative during first trimester
• Optimization of blood glucose levels during pregnancy for mothers with GDM or pre-existing diabetes
• Morphology scan at around 20 weeks in case of DM or GDM
• Fetal surveillance for growth parameters for DM or GDM

Peri-partum
• Close monitoring and maintain normoglycaemia
• Consider earlier delivery in cases with poor glycaemic control
• Consider elective Caesarian section for selective cases with macrosomia

After delivery
• For GDM mothers, post-partum oral glucose tolerance test at 6 weeks after delivery to exclude pre-existing DM
• Exclusive breast feeding should be encouraged for at least 6 months (WHO policy)
• Avoid over-nutrition and monitor weight gain for offspring

Long-term prevention
• Active lifestyle modification
• Monitoring of offspring growth
Summary

• Epidemic of diabetes and obesity in Asia
• Emerging importance of intra-uterine environment and epigenetic changes
• Maternal diabetes and obesity are important risk factors for childhood obesity and metabolic disturbances
• Maternal DM, GDM and obesity may perpetuate a vicious cycle of “diabetes begetting diabetes”
• Optimal nutrition during pregnancy and interventions of high-risk women provide opportunity for prevention
Thank you

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