Gestational diabetes: finding your way through the minefield of controversy

Richard IG Holt
Professor in Diabetes & Endocrinology
16 February 2013 Diabetes Nepal, Kathmandu

Gestational Diabetes

- Defined as glucose intolerance appearing for the first time in pregnancy
  - Includes women with pre-existing but undiagnosed type 2 diabetes
- Commonest medical complication in pregnancy affecting 1-7% of women
  - ...and that's where the consensus stops!

Gestational Diabetes – a controversial area

- Diagnosis
- Screening
- Treatment

Brief History of GDM

- 1823: Bennewitz recorded 1st case of glucose intolerance in pregnancy
  - Resolved after 2 successive pregnancies
- 1940s: studies from Scotland and USA demonstrated increased perinatal mortality with lesser degrees of maternal hyperglycaemia
- 1954: 1st prospective study of glucose metabolism in pregnancy using 50g OGTT in Boston
- 1961: term “Gestational diabetes” used for the first time

Fetal Consequences

- Overgrowth of insulin sensitive tissues
  - Leads to macrosomia & Increased risk of shoulder dystocia
- Neonatal metabolic complications
  - Hypoglycaemia
  - Respiratory distress
- Fetal hypoxia
  - Still birth
  - Jaundice
- Long term risks
  - Obesity
  - Diabetes

Diagnostic dilemma

Glycaemia

Risk of Complication
### Gestational Diabetes Diagnostic Criteria

<table>
<thead>
<tr>
<th>Association</th>
<th>CHO 75g</th>
<th>≥1 readings</th>
<th>FBG 1-hr</th>
<th>2-hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>75g</td>
<td>≥1</td>
<td>7.0</td>
<td>7.8</td>
</tr>
<tr>
<td>ADA</td>
<td>100g</td>
<td>≥2</td>
<td>5.3</td>
<td>10.0</td>
</tr>
<tr>
<td>ADIPS</td>
<td>75g</td>
<td>≥1</td>
<td>5.5</td>
<td>8.0</td>
</tr>
<tr>
<td>CDA</td>
<td>75g</td>
<td>≥2</td>
<td>5.3</td>
<td>10.6</td>
</tr>
<tr>
<td>EASD</td>
<td>75g</td>
<td>≥1</td>
<td>6.0</td>
<td>9.0</td>
</tr>
<tr>
<td>NZSSD</td>
<td>75g</td>
<td>≥1</td>
<td>5.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

### Australian Carbohydrate Intolerance Study in Pregnant Women (ACOCHOIS)

- 1000 women identified with IGT with 2-hour 75g OGTT
  - 490 women allocated to treatment
  - 510 women with IGT to routine care
  - Women and HCP blinded to diagnosis
- Serious perinatal outcomes
  - Intervention group 1% v routine care 4%, p=0.01
- No significant difference between groups in maternal quality of life


### HAPO: Maternal Glucose & Birth Weight

- 23,116 women without diabetes
- Strong continuous relationship between maternal glucose and pregnancy outcomes
- No evidence of a threshold
- Levels below current diagnostic ranges are associated with worse outcomes

### The International Association of Diabetes and Pregnancy Study Groups

- Convened a conference to discuss the results in June 2008
- New diagnostic criteria proposed in March 2010

Diabetes Care. 2010 Mar;33(3): 676-82

### Basis of new criteria

- Thresholds determined as the values at which the ORs for adverse events were 1.75 fold higher than for women
  - Fasting glucose ≤4.5 mmol/L
  - 1-hr glucose ≤7.4 mmol/L
  - 2-hr glucose ≤6.2 mmol/L
- These were the mean values for the entire HAPO cohort
- ORs of 1.5 and 2.0 were also considered
### Comparison

<table>
<thead>
<tr>
<th>Association</th>
<th>CHO</th>
<th>No of high readings needed</th>
<th>FBG</th>
<th>1-hr</th>
<th>2-hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADPSG</td>
<td>75g</td>
<td>≥1</td>
<td>5.1</td>
<td>10.0</td>
<td>8.5</td>
</tr>
<tr>
<td>WHO</td>
<td>75g</td>
<td>≥1</td>
<td>7.0</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>100g</td>
<td>≥1</td>
<td>5.3</td>
<td>10.0</td>
<td>8.6</td>
</tr>
<tr>
<td>ADIPS</td>
<td>75g</td>
<td>≥1</td>
<td>5.5</td>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td>CDA</td>
<td>75g</td>
<td>≥2</td>
<td>5.3</td>
<td>10.6</td>
<td>8.9</td>
</tr>
<tr>
<td>EASD</td>
<td>75g</td>
<td>≥1</td>
<td>6.0</td>
<td></td>
<td>9.0</td>
</tr>
<tr>
<td>NZSSD</td>
<td>75g</td>
<td>≥1</td>
<td>5.5</td>
<td></td>
<td>9.0</td>
</tr>
</tbody>
</table>

**GDM Diagnoses within HAPO**

- % 8.3
- % 14
- % 16.1
- % 17.8

Diabetes Care. 2010 Mar;33(3):676-82

### Effect in Southampton

- Approx. 5800 births per annum in Southampton
- Between January 2002 and May 2003, 1260 OGTTs were performed
- 103 met WHO criteria for GDM
  - 8.2% of tests
  - Overall prevalence 1.25%
- Applying IADPSG criteria
  - 185 meet criteria
  - 14.8% of test
  - Overall prevalence 2.25% (80% increase)


### Effect on clinics

- Marked increase in women with less degrees of hyperglycaemia
- May adversely affect those with more severe disease

### How are we dealing with diagnostic change?

- Women whose FBG is between 5.1 – 7.0 mmol/L receive targeted and specific lifestyle advice
- Otherwise normal pregnancy management
- Is this justified?

**Maternal-Fetal Medicine Units Network Trial**

- 938 Pregnant women were screened with a 50g GCT
  - 100g OGTT if 1-hr glucose 7.5-11.1 mmol/L
- Eligible for study if:
  - FBG <5.3 mmol/L and ≥2 abnormal post-glucose values
  - 1-hr >10 mmol/L, 2-hr >8.6 mmol/L, 3-hr >7.8 mmol/L
  - If glucose exceeded these values, then GDM diagnosed and women had routine care
- Randomised to glucose monitoring, ± insulin vs. routine care

MFMU trial results

- No significant difference in composite primary outcome of serious perinatal outcome or individual components
- Intervention led to significant reductions in
  - Birth weight 3302 vs. 3408g
  - Caesarean section 26.9% vs. 33.8%
  - Shoulder dystocia 1.5% vs. 4.0%
  - Pre-eclampsia 2.5% vs. 5.5%
  - Maternal hypertension

Landon NEJM 2009 361(14): 1339-1348

Gestational Diabetes – a controversial area

- Diagnosis
- Screening
- Treatment

Screening for GDM

Universal diagnostic test (IADPSG)

VS

Selective screening by risk factors (NICE)
e.g. previous hx of GDM, FH of DM, obesity

Southampton experience

- Incidence in Southampton 1.6%
  - Genuine low incidence in Southampton
  - Wrong Screening Policy
  - Incomplete compliance with Screening Policy
- Audit showed significant misunderstanding of GDM and screening criteria
  - Re-design of GDM 75g OGTT test form
- Re-audit
  - Much better understanding
  - 30% more OGTT in following year
  - No change in diagnosis rate

Diabet Med. 2005 Apr;22(4):507-8

NICE cost effectiveness analysis

- Incremental cost effectiveness ratio (ICER) for different strategies:
  - High-risk ethnic backgrounds £3,678
  - Women defined by ADA at high risk of GDM £21,739
    - Age >25 years
    - BMI >27kg/m²
    - Family history of diabetes
    - High-risk ethnic background
  - BMI £12,737
  - Family history £5,209
- Threshold of £20,000 per QALY for NICE

Caveat

- Best approach will depend on:
  - Prevalence of gestational diabetes
  - Prevalence of undiagnosed type 2 diabetes
  - Resources available
Gestational Diabetes – a controversial area

- Diagnosis
- Screening
- Treatment

Glycaemic Control in GDM

- Intensive (n=1316) v conventional glycaemic (n=1145)
  - Monitoring 7x/ day v 4x/ day
  - Mean glucose in intensive group 5 ± 2 mmol/L

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSCS</td>
<td>13%</td>
<td>19%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>7.1%</td>
<td>13.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IOL</td>
<td>22%</td>
<td>27%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>3.7 days</td>
<td>4.3 days</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NNU</td>
<td>6.3%</td>
<td>25%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


Glycaemic Targets

- The lower the average glucose, the better the outcome
  - Aim for FBG 3.5 – 6.0 mmol/L
  - Post-prandial <7.8 mmol/L

Oral Agents in Gestational Diabetes

- Important with increasing number of pregnant women with T2DM
- Potential advantages
  - Cheaper
  - Less clinic resources needed
  - More convenient & less painful
  - Better control
  - Fewer hypoglycaemic episodes

1st generation sulphonylureas

Contra-indicated

- Fetal hyperinsulinaemia
  - Macrosomia
  - Neonatal hypoglycaemia
- Increased perinatal mortality
- Increased congenital malformations
  - Association between 1st trimester SU & major congenital malformations
  - Confounding because of metabolic control

Why glibenclamide?

- Placental transport of oral hypoglycemic agents varies markedly
- Glibenclamide shows no transfer in re-circulating single cotyledon human placenta model

**Langer Trial**

- 404 women with GDM (ADA criteria)
- Randomised to receive glibenclamide or insulin
- Equivalent glycaemic control
  - 82% of glib women v 88% of insulin women
  - 8/201 (4%) converted to insulin
  - Fewer hypos with glib (4) v insulin (41)
- No difference in birth or neonatal outcomes
- Glibenclamide not found in cord blood


**Southampton Experience with Glibenclamide**

- 77 women have been treated with glibenclamide between March 2004 – March 2008
  - Mean Dose 7.3 ± 0.8 mg, Median 5 mg
  - Higher proportion of Asian women
- 68% achieved control with glibenclamide
- Compared with women treated with insulin, women treated with glibenclamide had:
  - No difference in mode of delivery or birth size
  - No difference in neonatal complications with the exception of high number with neonatal jaundice
- Non-responders had higher BMI
- Women (esp non-white European) valued the choice

Holt et al Diabetes, Obesity and Metabolism 2008 10(10) 906-11

**Metformin in Pregnancy**

- No evidence of teratogenicity
- Increasingly used in PCOS
  - Facilitates conception
  - Decreases miscarriage rate
  - Reduces GDM


**Metformin in Gestational Diabetes study**

- RCT of GDM women
  - Treated with MTF (n=373) or Insulin (n=378)
- Dose 500-2500mg daily
- Targets
  - FBG <5.5 mmol/L
  - PPG <7.8 mmol/L


**Metformin in Gestational Diabetes study**

- 46% needed additional insulin but dose lower than with insulin alone
- Primary composite outcome of neonatal hypoglycaemia, respiratory distress, phototherapy, birth trauma, low APGAR and prematurity
  - No different between groups
  - Prematurity 12.1% v 7.6% (x diff was 1.7 days)
  - Birth weight similar
- Side Effects in ~10%
  - Less weight gain with MTF
  - Higher patient satisfaction


**Glibenclamide or MTF**

<table>
<thead>
<tr>
<th>Glibenclamide</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieves glycaemic control in ~70%</td>
<td>Achieves glycaemic control in ~50%</td>
</tr>
<tr>
<td>Switch to insulin possible</td>
<td>Addition of insulin easy</td>
</tr>
<tr>
<td>No difference in weight compared with insulin</td>
<td>Less weight gain</td>
</tr>
<tr>
<td>?More jaundice</td>
<td>?Increased prematurity</td>
</tr>
<tr>
<td>Well liked by women</td>
<td>Well liked by women</td>
</tr>
</tbody>
</table>
NICE guidance
Pharmacological treatment of GDM

• Hypoglycaemic therapy for women with GDM (which may include regular insulin, rapid-acting insulin analogues [aspart and lispro] and/or hypoglycaemic agents [metformin & glibenclamide] should be tailored to the glycaemic profile of, & acceptability to, the individual woman.

Conclusions

• GDM is an important diagnosis to make
  – but cut-off levels vary

• Risk factor based screening appears optimal in the UK but this may not be appropriate for Nepal

• Oral hypoglycaemic agents may offer a safe and acceptable alternative to insulin

Any questions?