Gestational Diabetes in Resource Limited Area

Prof Satyan Rajbhandari (RAJ)
Case History

- RP, 26F
- Nepali girl settled in the UK
- Primi Gravida
- BMI: 23
- FH of type 2 DM
75 gm Glucose OGTT in week 25

0 Min     5.4 mmol (97 mg%)
120 Min   8.6 mmol (155 mg%)

Gestational DM
Referral to specialist clinic
Self blood glucose monitoring
Diabetes Pregnancy Clinic

- Low Glycaemic carbohydrate
- Blood glucose monitoring up to 8 times a day
- Close monitoring by Diabetes Nurse & Dietician
- Monthly appointment in clinic
Follow up

- Post prandial blood glucose 8.2 (148 mg%) towards week 30
- Started on Humalog before each meal
- Normal delivery at week 39. Needed IV insulin infusion during delivery
- No maternal or fetal complication
- Maternal fasting glucose normal at 6 weeks
Gestational diabetes

"Carbohydrate intolerance of varying degrees of severity, with onset or first recognition during pregnancy"
Metabolic changes in pregnancy

- Increased insulin resistance
  - Due to hormones secreted by the placenta that are “diabetogenic”:
    - Growth hormone
    - Human placental lactogen
    - Progesterone
    - Corticotropin releasing hormone
  - Transient maternal hyperglycemia occurs after meals because of increased insulin resistance
Metabolic changes in pregnancy

Relative baseline hypoglycemia

- Proliferation of pancreatic beta cells (insulin-secreting cells) leads to increased insulin secretion
  - Insulin levels are higher than in pregnant than nonpregnant women in fasting and postprandial states

- Hypoglycemia between meals and at night because of continuous fetal draw
  - Blood glucose levels are 10-20% lower
Gestational Diabetes

Non-pregnant

- Insulin secretion
- Insulin Resistance

Pregnant

- Insulin secretion
- Insulin Resistance
Short-term complications

- Complications in pregnancy
  - Hypertension, pre-eclampsia, preterm delivery
- Complications during labour
  - Shoulder dystocia, C-section, maternal lesions
- Neonatal morbidity
  - Hypoglycaemia, prematurity, jaundice, RDS
- Neonatal mortality - rare

macrosomia
Macrosomia and shoulder dystocia

- High sugars induce fetal insulin production
- Extra fat deposition
- Extra growth of all tissues
- Shoulder areas bigger than the head
- Shoulder dystocia
Screening for GD

- Universal testing with OGTT (oral glucose tolerance test)
- Selective testing with OGTT
  - Glucosuria
  - Age
  - BMI
  - Diabetes in first degree relatives
  - Previous GDM
# GDM Criteria

<table>
<thead>
<tr>
<th></th>
<th>National Diabetes Data Group*</th>
<th>American Diabetes Association*</th>
<th>WHO †</th>
<th>Carpenter and Coustan*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>105</td>
<td>95</td>
<td>$\geq 126$</td>
<td>95</td>
</tr>
<tr>
<td>1 hour</td>
<td>190</td>
<td>180</td>
<td>-</td>
<td>180</td>
</tr>
<tr>
<td>2 hours</td>
<td>165</td>
<td>155</td>
<td>$\geq 140$</td>
<td>155</td>
</tr>
<tr>
<td>3 hours</td>
<td>145</td>
<td>140</td>
<td>-</td>
<td>140</td>
</tr>
</tbody>
</table>

*2 or more criteria met = positive diagnosis  (cutoff points in mg/dl)

† 1 or more criteria met = positive diagnosis
Background: prevalence

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>5%</td>
</tr>
<tr>
<td>UK</td>
<td>3.5%</td>
</tr>
<tr>
<td>CANADA</td>
<td>3%</td>
</tr>
<tr>
<td>USA (South Asian)</td>
<td>14%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3.5%</td>
</tr>
<tr>
<td>India</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

Increasing prevalence due to Obesity, urbanisation and late age of pregnancy
HAPO study

Aim

- To clarify unanswered questions on associations of maternal glycemia, less severe than overt diabetes mellitus, with risks of adverse pregnancy outcome

Methods

- Observational multicenter study (N=25,000)
- Inclusion: FPG<5.8 mmol/l and 2-h PG <11 (75 g OGTT wk 24-32)
- Blinding of OGTT results

Int J Gyn Obstet 2002 78(1):69-77
LGA infants

%  
30  25  20  15  10  5  0  
1  2  3  4  5  6  7  
HAPO glucose categories

Hapo N Engl J Med 08

- fasting
- 1 h
- 2 h
Management of GDM

- Diet treatment
- Exercise
- Self monitoring of blood glucose (SMBG)
- Pharmacological treatment
- Close obstetric surveillance
SMBG - therapeutic goals

<table>
<thead>
<tr>
<th></th>
<th>ADA (American Diabetes Association)</th>
<th>ACHOIS (Australian Carbohydrate Intolerance Study in Pregnant Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BG</td>
<td>PG*</td>
</tr>
<tr>
<td>Faste</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>1h ppr.</td>
<td>7.8</td>
<td>8.7</td>
</tr>
<tr>
<td>2h ppr.</td>
<td>6.7</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Therapeutic goal: HbA1c < 5.6%
Dietary treatment

- Self-management therapy - SMBG
- Secure micronutrients
- Energy restriction of 30% in obese women
  - Reduced glucose and TG with no increase in ketonuria (Franz MJ et al. Diabetes Care 17:490–518, 1994)
- Carbohydrate restriction (35-40% of energy)
  - better glycaemic control, reduced rates of macrosomia and CS (Major CA et al. Obstet Gynecol 91:600–604, 1998)
Exercise

- Increase insulin sensitivity
- Improve maternal glycaemic control
  (Jovanovic-Peterson *AJOG* 1989, Brankston *AJOG* 04)
  - Recent Cochrane review found no effect of exercise alone compared to other regimens
- Prevent GDM (Dempsey *Am J Epidemiol* 04)
Obstetric care

- Treatment of hypertension and preeclampsia
  - Methyldopa, labetalol, ASA
- Clinical and ultrasonographic surveillance for fetal size and wellbeing
- Timing of delivery 38-40 gestational week
Does treatment of GDM improve outcome?

- **Intervention group, N=490**
  - informed they had “glucose intolerance of pregnancy”
  - SMBG, diet, insulin, intensified obstetric surveillance

- **Control group, N=510**
  - informed they “did not have gestational diabetes”
  - Routine obstetric management

*Crowther et al. NJEM 2005;352:2477-2486*
### Serious perinatal outcome:
Perinatal death and shoulder dystocia

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N 506)</th>
<th>Routine care (N 526)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious perinatal outcome</td>
<td>7 (1%)</td>
<td>23 (4%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>

NNT = 34

NJEM 2005;352:2477-2486
## Infant outcome

<table>
<thead>
<tr>
<th></th>
<th>Int. group (N 506)</th>
<th>Rout.Gr. (N 526)</th>
<th>Adj. Treatment effect or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3335</td>
<td>3482</td>
<td>-145 (-219 to -70)</td>
</tr>
<tr>
<td>LGA</td>
<td>13%</td>
<td>22%</td>
<td>0.62 (0.47-0.81)</td>
</tr>
<tr>
<td>4000g</td>
<td>10%</td>
<td>21%</td>
<td>0.47 (0.34-0.64)</td>
</tr>
<tr>
<td>SGA</td>
<td>7%</td>
<td>7%</td>
<td>0.88 (0.56-1.39)</td>
</tr>
<tr>
<td>Apgar 5&lt;7</td>
<td>1%</td>
<td>2%</td>
<td>0.57 (0.21-1.53)</td>
</tr>
<tr>
<td>Hypoglyc.</td>
<td>7%</td>
<td>5%</td>
<td>1.42 (0.87-2.32)</td>
</tr>
<tr>
<td>RDS</td>
<td>5%</td>
<td>4%</td>
<td>1.52 (0.86-2.71)</td>
</tr>
</tbody>
</table>

Mean±SD, median (IQ NJEM
Summary

Diagnosis and treatment of GDM:

- Reduces the risk of serious perinatal complications by 75%
- Reduces the risk of macrosomia by 50%
Pharmacological treatment

- **SAFE**
  - Insulin (human and fast acting analogues)

- **MAYBE SAFE**
  - Glyburide (glibenclamide)
  - Metformin
  - Arcabose

- **NOT SAFE**
  - Most sulfonylureas (prolonged neonatal hypo)
  - Thiazolidinediones TZD (teratogenicity)
Insulin regimens

- Basal-bolus regimen
- Premixed insulin
- Bolus only
- Others
## Twice vs. four times daily insulin in gestational diabetes

<table>
<thead>
<tr>
<th></th>
<th>Insulin * 2</th>
<th>Insulin * 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>136</td>
<td>138</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.8</td>
<td>5.5*</td>
</tr>
<tr>
<td><strong>Adequate control (%)</strong></td>
<td>74</td>
<td>91*</td>
</tr>
<tr>
<td><strong>Macrosomia (&gt;4000 g)</strong></td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td><strong>Neonat- hypoglycaemia</strong></td>
<td>8</td>
<td>1*</td>
</tr>
<tr>
<td><strong>Overall neonat morbidity</strong></td>
<td>40</td>
<td>24*</td>
</tr>
</tbody>
</table>

Nachum BMJ
Rationale for glyburide

- Potential risk of SU in pregnancy
  - Prolonged neonatal hypoglycemia
  - Teratogenicity
- Placental passage of glyburide minimal in perfusion studies
- No need for injection
- Insulin more expensive
## Glyburide vs. insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Glyburide (N=201)</th>
<th>Insulin (N=203)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA (%)</td>
<td>24 (12)</td>
<td>26 (13)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypoglycaemia (%)</td>
<td>18 (9)</td>
<td>12 (6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stillbirth (%)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5 ± 0.7</td>
<td>5.4 ± 0.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Means ± SD

Langer et al. NEJM 2000, 343;1135-38
Metformin in pregnancy

- Potential risks:
  - Teratogenity or less malformations
  - Lactic acidosis
  - Still birth (Helmuth, Diab Med 2000)
  - Neonatal hypoglycemia
## Metformin vs insulin in GDM

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>363</td>
<td>388</td>
</tr>
<tr>
<td><strong>Composite poor outcome</strong></td>
<td>32 %</td>
<td>32 %</td>
</tr>
<tr>
<td><strong>Insulin supplemented</strong></td>
<td>46%</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Women prefer metformin

Rowan, N Engl, J Med 08
Long-term complications of GDM

- **Mother**
  - Diabetes up to 70 %
  - Obesity
  - Cardiovascular disease

- **Offspring**
  - Glucose intolerance incl. GDM
  - Other metabolic risk factors
  - Other morbidity
Born big may not be better

- Intra uterine excess food intake
- Risk of future obesity
- Risk of future diabetes
GDM in Nepal
### WHO Criteria for screening

<table>
<thead>
<tr>
<th>Criteria</th>
<th>FPG mg/dl (mmol/L)</th>
<th>2-hr PG mg/dl (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Glucose Tolerance [NGT]</td>
<td>&lt; 108 (6)</td>
<td>&lt; 140 (7.7)</td>
</tr>
<tr>
<td>Impaired Fasting Glucose [IFG]</td>
<td>108 – 125 (6.1 – 6.9)</td>
<td>-</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance [IGT] &amp; Gestational Diabetes</td>
<td>-</td>
<td>140 – 199 (7.8 – 11)</td>
</tr>
<tr>
<td>Diabetes Mellitus [DM]</td>
<td>126 (7) &amp; / or</td>
<td>&gt; 200 (11.1)</td>
</tr>
</tbody>
</table>
Universal screening in Nepal (24-28 weeks)

- Should be a part of standard antenatal care
- No need for fasting if it is not practical
- 75g oral glucose load (5 tea spoons of sugar) without regard to the time of the last meal
- A venous blood sample is collected at 2 hours for estimating plasma
- Blood sugar above 140 (7.8) is GDM
Metformin as first line drug

- If not controlled by Diet & exercise
- Cheap
- No risk of hypoglycaemia
- As safe as Insulin
- No need for injections
- Patients prefer Metformin to insulin
Monitoring in Pregnancy

- Combined diabetes antenatal clinic with obstetricians
- Monitor Weight, blood pressure
- Fasting and 1 hour post prandial blood glucose
- Start second line treatment if blood glucose not controlled
Second line treatment

- Insulin if patients can monitor blood glucose at home
  - Long acting if fasting raised
  - Short acting if postprandial raised
- Glibenclamide if unable to monitor
Preparing for Delivery
Management of Labour

- Close link with Obstetrician
- Delivery before full term not indicated because of GDM
- Elective induction if pregnancy > 40W
- Monitor maternal blood glucose & IV insulin if needed
- Stop IV insulin after 2nd stage of labour
Following Delivery
Post Partum

- Stop Oral hypoglycaemics or Insulin for mothers but monitor blood sugars
- Monitor for other neonatal complications (RDS, hyperbilirubinaemia)
- Monitor neonatal capillary blood glucose 1, 2 & 4 hour after birth to maintain it above 46 mg% (2.6 mmol/L).
- Encourage early breast feeding
Long term Management

- Up to 80% risk of GDM in subsequent pregnancy
- Seven fold risk of diabetes
  - Diet
  - Exercise
  - Weight reduction
  - CV risk
- Suggest annual fasting blood glucose or HbA1c check up