Gestational Diabetes Mellitus

SpR Study Day
Maternal Medicine
Withybush General Hospital Haverfordwest
20 April 2012

Mr Richard Husicka
carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy

(whether or not insulin is used and regardless of whether diabetes persists after pregnancy)
Incidence of DM in pregnancy

- 3-6% pregnancies with DM in England & Wales
  - around 65,000 births/year
- Pre-existing DM 0.37% (12.5% of DM in pregnancy)
  - Type 1 - 7.5%
  - Type 2 - 5%
- GDM 3.5% in E&W (87.5% of DM in pregnancy)
  - True GDM
  - Pre-existing DM (1:1000)


Clinical features of GDM

- **Asymptomatic**
  - develops in the 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester

- **Diagnosed by**
  - routine biochemical screening
  - or after suspicious findings
    - macrosomia, polyhydramnios, persistent glycosuria, recurrent infections

- **Rarely diagnosed retrospectively**
  - after IUD
  - birth of macrosomic baby
    - random plasma glucose or HbA1c
Impact of GDM on pregnancy

- increased perinatal morbidity and mortality
  - same way but to a much lesser degree than pre-existing DM

- maternal hyperglycaemia
  - excess transfer of glucose to the fetus
  - fetal hyperinsulinaemia

Fetal hyperinsulinaemia

- An overgrowth of insulin sensitive tissue
  - adipose tissue – chest, shoulders, abdomen
  - shoulder dystocia, birth trauma, CS, perinatal death
- Neonatal metabolic complications
  - hypoglycaemia, RDS, hypocalcemia
- A hypoxaemic state in utero
  - risk of IUD, polycythaemia, hyperbilirubinaemia and renal vein thrombosis


What to tell women?

- All women
  - healthy diet, optimal body weight, exercise

- Women with risk factors
  - explain the nature of GDM and impact on pregnancy
  - risks
  - importance of the screening
  - advantages of having GDM diagnosed
Screening and diagnosis

- Original work by O’ Sullivan (1964)
  - 100g oral glucose challenge test
    

- Key questions:
  - What level of maternal hyperglycemia measurably worsens pregnancy outcome?
  - Does intervention improve outcome?
  - Is such intervention cost effective?
  - What is the optimum screening and/or diagnostic test?

Diabetes in pregnancy
management of diabetes and its complications from preconception to the postnatal period

Clinical Guideline
March 2008 (revised reprint July 2008)
Funded to produce guidelines for the NHS by NICE
The 2 hour 75g oral glucose tolerance test (OGTT) should be used to test for GDM
- WHO criteria

Women with any risk factor
- OGTT at 24-28 weeks

GDM in previous pregnancy
- early self monitoring of blood glucose or
- OGTT at 16-18 weeks and
- OGTT at 28 weeks if results normal
The WHO definition of GDM encompasses both impaired glucose tolerance (IGT) and diabetes.

Table 4.1  World Health Organization criteria for the 75 g OGTT

<table>
<thead>
<tr>
<th></th>
<th>Whole blood venous</th>
<th>Whole blood capillary</th>
<th>Plasma venous</th>
<th>Plasma capillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>≥ 6.1 mmol/litre</td>
<td>≥ 6.1 mmol/litre</td>
<td>≥ 7.0 mmol/litre</td>
<td>≥ 7.0 mmol/litre</td>
</tr>
<tr>
<td>2 hours</td>
<td>≥ 6.7 mmol/litre</td>
<td>≥ 7.8 mmol/litre</td>
<td>≥ 7.8 mmol/litre</td>
<td>≥ 8.9 mmol/litre</td>
</tr>
</tbody>
</table>

IGT: fasting < 7.0 mmol/l, 2 hour ≥ 7.8 mmol/l  
Diabetes: fasting ≥ 7.0 mmol/l, 2 hour ≥ 11.1 mmol/l

Risk factors for GDM

- BMI > 30 kg/m²
- Previous baby ≥ 4.5 kg
- Previous GDM
- Family history of DM (first-degree relative with DM)
- Family origin with a high prevalence of DM:
  - South Asian
    - specifically women whose country of family origin is India, Pakistan or Bangladesh
  - Black Caribbean
  - Middle Eastern family origin
    - specifically Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt
Approximately 20–50% of women will have a positive screening result using these risk factors.

Proportions will be varying considerably from one geographical area to another.
Systematic review of 13 studies:

- **Non-white race/ethnicity**
  - most consistent predictor of future recurrence

- **Recurrence rates**
  - 52–69% in the minority ethnic populations
  - 30–37% in non-Hispanic white populations

Ethnic risk of GDM

- 11x in Indians
- 8x in South East Asians
- 6x in Arabs/Mediterraneans
- 3x in Afro-Caribbeans

- highest prevalence of GDM in inner city areas

* Nelson-Piercy C. Diabetes mellitus in Handbook of Obstetric Medicine, Fourth Edition, 2010*
Previous GDM and recurrence rate

- Recurrence of the GDM is 30–84%
- 75–77% in case of insulin-treatment in a previous pregnancy


Age – risk factor?

….. new research shows that maternal age, alone and in correlation with the maternal racial origin, may also be a significant factor contributing to the development of GDM.

Makgoba M, Savvidou M, Steer P. An analysis of the interrelationship between maternal age, body mass index and racial origin in the development of gestational diabetes mellitus. BJOG 2011; DOI: 10.1111/j.1471-0528.2011.03156.x.
Mike Marsh, Deputy Editor-in-Chief of BJOG:
“It is crucial that women are aware of the benefits of healthy eating and weight control prior to pregnancy as this may reduce the risk of them developing diabetes in pregnancy. Avoiding being overweight prior to pregnancy is particularly important for older women of South Asian and Black African racial origin.”
Does treatment help?

- **ACHOIS trial**
  - RCT, 2005 (GDM defined as per WHO)
  - 490 women with IGT in the treatment group
  - 510 women with IGT receiving routine care

- Treating GDM improves outcomes for women and babies
  - The rate of serious perinatal outcomes
    - 1% intervention group vs. 4% controls, \( P = 0.01 \)
  - 34 needed to treat to prevent a serious outcome in a baby

Counseling for GDM

- Good glycaemic control reduces risk of
  - fetal macrosomia
  - trauma during birth (to themselves and the baby)
  - induction of labour or caesarean section
  - neonatal hypoglycaemia and perinatal death


- The role of diet, body weight and exercise
  - may prevent or delay development of DM 2 in later life
    - risk doubled for each stone gained
    - risk 40-60% in next 10-15 years

Counseling - Blood glucose monitoring

- Blood glucose targets during pregnancy for women with DM (including GDM)
  - preprandial 3.5–5.9 mmol/l
  - 1 hour postprandial < 7.8 mmol/l
- Recommended self-monitoring of blood glucose
  - fasting blood glucose and 1 hour after meal
  - in insulin-treated DM advise to test blood glucose before going to bed at night

The goals - optimisation of glycaemic control

Avoid postprandial hyperglycaemia!

- an important aim of dietary therapy is reducing postprandial glucose levels

GDM - Diet

- 82% - 93% of women with GDM will achieve blood glucose targets on diet alone
  - carbohydrates from low glycaemic index sources
  - lean proteins including oily fish
  - balance of polyunsaturated fats and monounsaturated fats

- If BMI > 27 kg/m²
  - restrict calorie intake to 25 kcal/kg/day or less
    - does not result in ketonemia


Women with pre-existing DM will have received extensive advice about dietary management

Women with DM 1 will have been on a structured education course

- Dose Adjustment for Normal Eating (DAFNE)
- Offer course to those not trained as a matter of urgency
  - 6/12 after the course the mean HbA1c fell by 1%

Structured education programmes for DM 2

- X-PERT

**DAFNE Study Group.** Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746–8. doi:10.1136/bmj.325.7367.746

## Composition of the diet

### Dietary advice for pregnant women with DM

(modified from Nutrition Subcommittee of the Diabetes Care Advisory Committee of Diabetes UK)

<table>
<thead>
<tr>
<th>The composition of the diet</th>
<th>Nutritional advice for people with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Not &gt; 1 g per kg bodyweight</td>
</tr>
<tr>
<td>Total fat</td>
<td>&lt;35% of energy intake</td>
</tr>
<tr>
<td>Saturated +</td>
<td>&lt;10% of energy intake</td>
</tr>
<tr>
<td>transunsaturated fat</td>
<td></td>
</tr>
<tr>
<td>n-6 polyunsaturated fat</td>
<td>&lt;10% of energy intake</td>
</tr>
<tr>
<td>n-3 polyunsaturated fat</td>
<td>Eat fish, especially oily fish, once or twice weekly</td>
</tr>
<tr>
<td>Cis-monounsaturated fat</td>
<td>Fish oil supplements not recommended</td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>10–20% of energy intake</td>
</tr>
<tr>
<td>Sucrose</td>
<td>jointly 60–70% of energy intake</td>
</tr>
<tr>
<td>Fibre</td>
<td>45–60% of energy intake</td>
</tr>
<tr>
<td>Vitamins and antioxidants</td>
<td>Up to 10% of daily energy</td>
</tr>
<tr>
<td>Salt</td>
<td>No quantitative recommendation</td>
</tr>
<tr>
<td></td>
<td><em>Soluble fibre</em>: has beneficial effects on glycaemic and lipid metabolism</td>
</tr>
<tr>
<td></td>
<td><em>Insoluble fibre</em>: no direct effects on glycaemic and lipid metabolism but its high satiety content may benefit those trying to lose weight</td>
</tr>
<tr>
<td></td>
<td>Encourage foods naturally rich in vitamins and antioxidants</td>
</tr>
<tr>
<td></td>
<td>≤6 g sodium chloride per day</td>
</tr>
</tbody>
</table>

When to start hypoglycemic therapy?

- Diet and exercise fail to maintain blood glucose targets during a period of 1–2 weeks
- Ultrasound investigation suggests incipient fetal macrosomia
  - AC > 70th percentile

What treatment? NICE 2008

- Clinically effective therapy includes
  - oral agents (metformin and glibenclamide)
  - insulin therapy
    - regular human insulin or rapid-acting insulin analogues
- Health economic analysis
  - glibenclamide is cost-effective
    - lack of clinical evidence from NHS setting
    - RCT investigating metformin is due to report (MiG)
- Therapy should be individually tailored

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Treatment - Oral agents (update)

- **Glibenclamide (Glyburide)**
  - shorter-acting sulfonylurea
  - in 2000 - same outcomes as insulin treatment (4% switched to insulin)
    - safe for most GDM and some DM 2
    - less episodes of hypoglycaemia than insulin and more convenient
  - new RCT 2010
    - women with GDM randomised to metformin or glibenclamide
    - 35% of the metformin group required insulin
    - 16% of the glibenclamide group required insulin


Treatment - Oral agents (update)

- **MiG trial 2008  Metformin – biguanide**
  - safe and effective in GDM in the second half of pregnancy
  - perinatal outcomes similar
  - lower incidence of
    - PIH, pre-eclampsia, hypoglycaemia
  - lower postprandial glucose, lower maternal weight
  - 46% needed insulin to achieve adequate control

- **With lower glycaemic targets achieved = less complication**
  - birth weight >4kg, pre-eclampsia, prematurity

- **Follow-up after 2 years**
  - better subcutaneous to visceral fat ratio

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Rowan JA et al. *Diabetes Care* 2011;34:2279
Rapid-acting insulin analogues
- aspart and lispro – benefits compared with regular insulin outside pregnancy (also demonstrated in the pregnant population)
  - fewer episodes of hypoglycaemia
  - reduction in postprandial glucose excursions
  - improvement in overall glycaemic control

Long-acting insulin analogues
- Still unclear safety of the long actin insulin analogue – glargin
- isophane insulin (NPH) remains the first choice in pregnancy
Insulin regimen

- **RCT (392 patients)**
  - insulin four times daily vs. insulin twice daily
  - four-times-daily insulin
    - improves glycaemic control and perinatal outcomes
    - does not increase the risks of maternal hypoglycaemia and caesarean section

- **CSII**
  - should be offered if adequate control is not obtained without disabling hypoglycaemia

- In insulin-treated DM - provide concentrated glucose solution
  - in type 1 DM give also glucagon

Fetal growth and wellbeing

- USS 4 weekly
  - fetal growth and AFI from 28 to 36 weeks
- Monitoring of fetal wellbeing before 38 weeks is not recommended (unless IUGR)
- Contact with the diabetes care team every 1–2 weeks throughout pregnancy

Preterm labour and DM

- Steroids and tocolysis can be used
  - additional insulin and close monitoring if treated by steroids
    - sliding scale vs. outpatient regimes
  - betamimetic drugs should not be used for tocolysis

Timing and mode of birth

- Elective IOL or CS (if indicated) after 38 weeks
  - if uncomplicated pregnancy
  - reduces the risk of stillbirth and shoulder dystocia
  - does not increase CS rate
- VBAC – no contraindication
- Macrosomia
  - discuss the risks and benefits of vaginal birth, IOL and CS

Hyperglycaemia intrapartum

- Risk of fetal hypoglycaemia post partum
  - response to poorly controlled DM
  - response to maternal hyperglycaemia during the labour
- Maternal hyperglycaemia associated with fetal distress
- CEMACH
  - 47% of the women with DM 1 and 41% with DM 2 had sub-optimal glycaemic control during labour and birth ($P = 0.28$)

Glycaemic control during labour and birth

- **Women with DM**
  - monitor capillary blood glucose on an hourly basis
  - aim for blood glucose 4 - 7 mmol/l

- **Women with DM 1**
  - i.v. dextrose and insulin if blood glucose is not 4 - 7 mmol/l

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Post partum - Breastfeeding

- Breastfeeding
  - probably doesn't affect glycaemic control
    - no high-quality studies
  - lower FBG 6/52 post partum in those exclusively breastfeeding
    - compared with those who stopped breastfeeding before 6/52 post partum or with those who bottle-fed

Post partum - Management

- **GDM**
  - stop hypoglycaemic treatment immediately after birth

- **Insulin-treated pre-existing DM**
  - reduce insulin immediately after birth and monitor blood glucose levels carefully to establish the appropriate dose
  - inform about risk of hypoglycaemia in the postnatal period
    - especially when breastfeeding
    - advise to have a meal or snack available before or during feeds

- **DM 2 and breastfeeding**
  - can resume or continue to take metformin/glibenclamide immediately
    - but other oral hypoglycaemic agents should be avoided while breastfeeding

- **Women with diabetes who are breastfeeding**
  - avoid any drugs for the treatment of DM complications that were discontinued for safety reasons in the preconception period

Follow-up after birth

- **Pre-existing DM**
  - refer back to their routine diabetes care arrangements

- **GDM**
  - exclude persisting hyperglycaemia before transfer to community care
  - remind of the symptoms of hyperglycaemia
  - offer lifestyle advice
    - including weight control, diet and exercise
  - FBG 6/52 post partum and annually thereafter
  - inform about the risks of GDM in future pregnancies
  - screening for DM when planning future pregnancies
    - OGTT or fasting plasma glucose
  - early blood glucose self-monitoring or an OGTT in future pregnancies
    - subsequent OGTT at 28/40 if normal results
Planning of pregnancy

- importance of contraception
- need for preconception care
The multinational Hyperglycaemia and Pregnancy Outcome (HAPO) study

- defined the relationship of maternal glucose tolerance to neonatal outcomes in over 23,000 women
- linear relationship between maternal fasting and postprandial glucose level and birth weight above 90th centile
- same apply to adiposity
- no apparent threshold effect

The International Association of Diabetes and Pregnancy Study Groups

- consensus report 2010
  - effort to achieve international consensus
  - radical redrawing of diagnosis and screening

<table>
<thead>
<tr>
<th></th>
<th>WHO/NICE</th>
<th>IADPSG†</th>
<th>Above IADPSG threshold (cumulative %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting 75 g OGTT</td>
<td>≥7.0 mmol/l</td>
<td>≥5.1 mmol/l</td>
<td>8.3</td>
</tr>
<tr>
<td>1 hour</td>
<td>–</td>
<td>≥10.0 mmol/l</td>
<td>14.0</td>
</tr>
<tr>
<td>2 hour</td>
<td>≥7.8 mmol/l</td>
<td>≥8.5 mmol/l</td>
<td>16.1‡</td>
</tr>
</tbody>
</table>

- dg levels set at the levels of blood glucose at which adverse outcomes (LGA, cord C peptide and newborn fat >90th C) are increased 1.75 fold over the mean from HAPO test for all population
- expected incidence of GDM over 16% !!!

Update since NICE 2008 guideline - SIGN

- Scottish guidelines adopted IADPSG criteria
  - oGTT for high risk women
  - fasting glucose for low risk women

Current challenges

- How to translate the results of trials into the practice?
  - probably no more studies without dg or treatment of diabetes
- Major increase in incidence
  - but probably only 8-20% would need insulin or oral treatment
- Can we indicate
  - high risk women for intensive intervention?
  - low risk group which does not need testing?
- Dietary changes in larger proportion of pregnant women
  - Would it be beneficial?
  - Would it prevent GDM and complications?
- Can we influence the health of the next generation?