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# Gestational diabetes: finding your way through the minefield of controversy

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## 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!

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## Gestational Diabetes – a controversial area

- Diagnosis
- Screening
- Treatment

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## 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

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## 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

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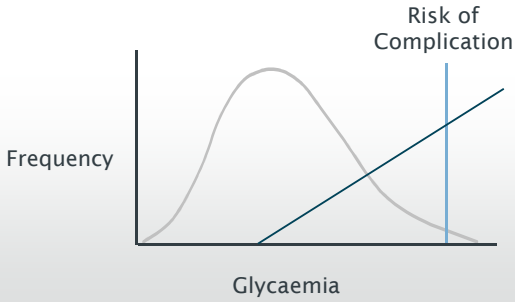
## Diagnostic dilemma

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## Gestational Diabetes Diagnostic Criteria

| Association | CHO | No of high readings needed | FBG | 1-hr | 2-hr |
|---|---|---|---|---|---|
| **WHO** | **75g** | **≥1** | **7.0** | | **7.8** |
| ADA | 100g | ≥2 | 5.3 | 10.0 | 8.6 |
| ADIPS | 75g | ≥1 | 5.5 | | 8.0 |
| CDA | 75g | ≥2 | 5.3 | 10.6 | 8.9 |
| EASD | 75g | ≥1 | 6.0 | | 9.0 |
| NZSSD | 75g | ≥1 | 5.5 | | 9.0 |

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

- 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

Crowther et al. N Eng J Med 2005; 352:(24) 2477-86.

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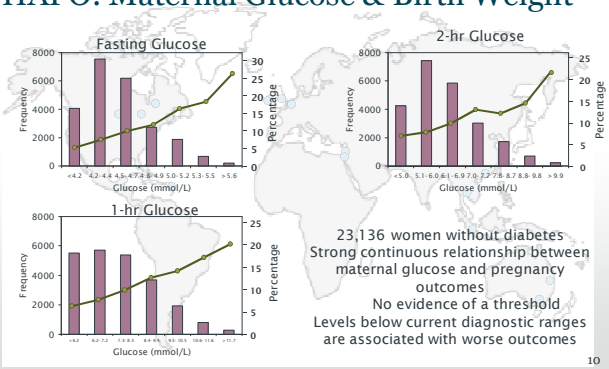
## HAPO: Maternal Glucose & Birth Weight




HAPO study group NEJM 2008

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## 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

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## 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

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## Comparison

| Association | CHO | No of high readings needed | FBG | 1-hr | 2-hr |
|---|---|---|---|---|---|
| **IADPSG** | **75g** | **≥1** | **5.1** | **10.0** | **8.5** |
| WHO | 75g | ≥1 | 7.0 | | 7.8 |
| ADA | 100g | ≥2 | 5.3 | 10.0 | 8.6 |
| ADIPS | 75g | ≥1 | 5.5 | | 8.0 |
| CDA | 75g | ≥2 | 5.3 | 10.6 | 8.9 |
| EASD | 75g | ≥1 | 6.0 | | 9.0 |
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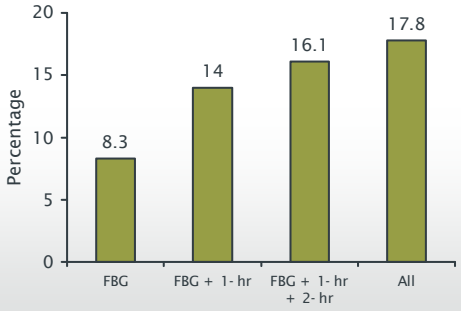
## GDM Diagnoses within HAPO




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

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## 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)

Holt et al Diabet Med. 2011 Apr;28(4):382-5

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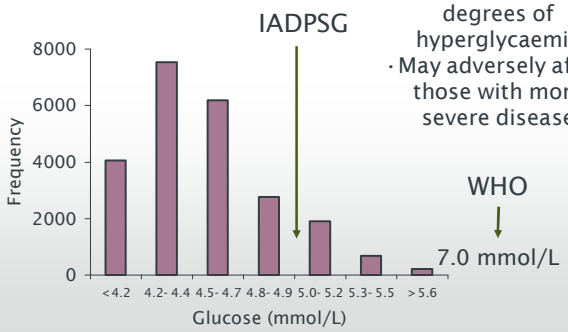
## Effect on clinics

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

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## 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?

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## Maternal-Fetal Medicine Units Network Trial

- 958 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

Landon et al N Engl J Med. 2009 Oct 1;361(14):1339-48

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## 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

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## Gestational Diabetes – a controversial area

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## Screening for GDM

Universal diagnostic test (IADPSG)

VS

Selective screening by risk factors (NICE)

e.g. previous hx of GDM, FH of DM, obesity

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## 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

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## 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

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## Caveat

- Best approach will depend on:
  - Prevalence of gestational diabetes
  - Prevalence of undiagnosed type 2 diabetes
  - Resources available

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## 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

| | Intensive | Conventional | P value |
|---|---|---|---|
| LSCS | 13% | 19% | p<0.01 |
| Macrosomia | 7.1% | 13.6% | p<0.0001 |
| IOL | 22% | 27% | p<0.01 |
| Hospital Stay | 3.7 days | 4.3 days | p<0.01 |
| NNU | 6.3% | 25% | p<0.0001 |

Langer et al. Am J Obstet Gynecol 1994; 170:(4)1036-46.

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## 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

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## 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

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## 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

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## Why glibenclamide?

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

Elliott et al. Am J Obstet Gynecol 1994 ;171(3):653-660
Elliott et al Am J Obstet Gynecol 1991;165(4 Pt 1):807-812

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## 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

Langer et al N Engl J Med. 2000 Oct 19;343(16):1134-8

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## 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

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## Metformin in Pregnancy

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

Glueck & Wang. Expert Opin Drug Saf. 2007 ;6(2):191-8

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## 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

Rowan et al N Engl J Med. 2008 May 8;358(19):2003-15

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## 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

Rowan et al N Engl J Med. 2008 May 8;358(19):2003-15

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## Glibenclamide or MTF

| Glibenclamide | Metformin |
|---|---|
| Achieves glycaemic control in ~70% | Achieves glycaemic control in ~50% |
| Switch to insulin possible | Addition of insulin easy |
| No difference in weight compared with insulin | Less weight gain |
| ?More jaundice | ?Increased prematurity |
| Well liked by women | Well liked by women |

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## 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.

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## 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

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# Any questions?