Diabetes and Pregnancy
Evidence-based clinical practice

Dr Bidhu Mohapatra, MBBS, MD, FRACP
Consultant Physician, Endocrinology and General Medicine
Bendigo Hospital
Adjunct Senior Lecturer, Monash University Medical School
Bendigo
Learning objectives

• Recognise the appropriate target level of glycaemic control for a woman with established diabetes before attempting to conceive

• Evaluate self-monitored blood glucose target levels for a woman with gestational diabetes and the appropriate therapeutic intervention if these targets are being exceeded

• Determine the appropriate frequency for ocular assessment for a pregnant woman with diabetes and known retinopathy

• Select appropriate antihyperglycaemic medication for a breastfeeding woman with type 2 diabetes
Diabetes and Pregnancy: Topics

- Preconception care of women with diabetes
- Gestation diabetes
- Glucose monitoring and glycaemic targets
- Blood glucose-lowering pharmacological therapy during pregnancy
- Nutrition therapy and weight gain targets for women with overt or gestational diabetes
- Labor, delivery, lactation and postpartum care
Diabetes and Pregnancy

Overt Diabetes

• Women diabetic before the onset of pregnancy
Current definition

Gestational Diabetes

• Any degree of glucose intolerance with onset or first recognition during pregnancy
Gestational Diabetes - Pathophysiology

- Insulin resistance emerging in the 2nd trimester of pregnancy
  - Progesterone
  - Cortisol
  - Human placental lactogen
  - Prolactin and estrogen also contribute

- Some pts. cannot balance insulin needs and develop GDM

- Placental insulinase enzyme and obesity
Preconception care of women with diabetes
Preconception care of women with diabetes

1.1 – Preconception counselling to all diabetic women

- Sufficient glycaemic control
- Assessment of comorbidities
- Discontinuing unsafe medications
- Folate supplementation
- Smoking cessation
Preconception care of women with diabetes

1.1 – Preconception counselling to all diabetic women

1. Better preconception glycaemic control

2. Lower rates of congenital anomalies and spontaneous abortions
Preconception care of women with diabetes

1.2 – Achieve blood glucose and HbA1c close to normal

Maternal hyperglycaemia in first few weeks of pregnancy

- Fetal malformations
- Spontaneous abortions
- Perinatal mortality
Preconception care of women with diabetes

1.2 – Achieve blood glucose and HbA1c close to normal

Congenital anomaly risk

HbA1c Levels
Preconception care of women with diabetes

1.3a – Insulin therapy

Multiple daily doses of insulin VS Split-dose, pre-mixed insulin therapy

1. More likely to achieve target levels
2. More flexible
Preconception care of women with diabetes

1.3b – Insulin therapy

- Change / Start insulin regimen in advance
  - Better expertise of patient
  - Optimisation
Preconception care of women with diabetes

1.3c – Insulin therapy

- Rapid-acting insulin analog vs Regular insulin
  
  ✔
  
  ☒
  
1. Achieve postprandial blood glucose targets better
2. Less risk of hypoglycaemia
3. Greater lifestyle flexibility and quality of life
4. Insulin lispro and insulin aspart safe in pregnancy
Preconception care of women with diabetes

1.3d – Insulin therapy
Continue Long-acting insulin analogs

<table>
<thead>
<tr>
<th>Long-acting insulin analog</th>
<th>VS</th>
<th>Intermediate-acting insulin analog</th>
</tr>
</thead>
</table>

1. Lower rates of nocturnal hypoglycaemia
2. Insulin glargine/detemir approved for use in pregnancy
Preconception care of women with diabetes

1.4 – Folic acid supplementation

• Start three months before conceiving
• 5mg daily dose

↓ Risk of neural tube defects
Preconception care of women with diabetes

1.5a – Ocular care (Endocrine Society 2013)

**Preconception care of women with diabetes**

1.5a – Ocular care (Endocrine Society 2013)
Preconception care of women with diabetes

1.5b – Ocular care (Endocrine Society 2013)

**Women with established retinopathy**

Ocular assessment every trimester

Post-pregnancy assessment within 3 months of delivery
Preconception care of women with diabetes

1.5c – Ocular care

Women with no retinopathy

Ocular assessment soon after conception

Then periodically as indication
Preconception care of women with diabetes

1.6 – Renal function

Renal dysfunction in T1DM = ↑ Risk of adverse maternal & fetal outcomes (e.g. pre-eclampsia)

Mild preconceptional renal dysfunction = Reversible worsening

Mod-severe preconceptional renal dysfunction = Irreversible worsening
Preconception care of women with diabetes

1.6a – Preconceptional renal function assessment

Regular renal function monitoring during pregnancy in women with preconceptional renal dysfunction
Preconception care of women with diabetes

1.7a Management of Hypertension

Satisfactory BP Control = <130 / 80 mmHg

Preconceptional renal dysfunction = ↑ Risk of adverse outcomes (e.g. pre-eclampsia)
Preconception care of women with diabetes

1.7b – Management of Hypertension

✔

• Methyldopa
• Labetalol
• Diltiazem
• Clonidine
• Prazosin

✗

• ACE Inhibitors
• ARBs
Preconception care of women with diabetes

1.7c – Management of Hypertension

Exception for using ACE Inhibitors or ARBS:
• Severe renal dysfunction with uncertainty about conception

Loss of renal protective properties vs Risk of teratogenesis
Preconception care of women with diabetes

1.7d – Management of Hypertension

If ACE Inhibitors or ARBs continued up to time of conception

Discontinue immediately upon confirmation of pregnancy
Preconception care of women with diabetes

1.8a – Elevated vascular risk

If vascular risk factors present

Screen for CAD before conceiving
Preconception care of women with diabetes

1.9 – Management of dyslipidaemia

1. Dyslipidaemia seldom poses threat during pregnancy

2. Unproven safety of statins, fibrates and niacin during pregnancy
Preconception care of women with diabetes

1.9 – Management of dyslipidaemia

1. DO NOT use statins

2. DO NOT use fibrates or niacin

3. Bile acid binding resins may be used to treat hypercholesterolaemia
Preconception care of women with diabetes

1.10 – Thyroid function assessment

- T1DM
  - Hypothyroidism
  - Autoimmune thyroid

Uncontrolled hypothyroidism

- ↓ Fertility
- ↑ Spontaneous abortion
- ↑ Impaired fetal brain development
Preconception care of women with diabetes

1.10 – Thyroid function assessment

• Serum TSH

• Thyroid peroxidase antibodies
Preconception care of women with diabetes

1.11 – Weight reduction in overweight/obese

Severe calorie restriction (<1500 kcal/day or 50% reduction)

↑ Ketosis

Impaired fetal brain development

Moderate calorie restriction (1600 - 1800 kcal/day or 30% reduction)

No ketosis

Optimal fetal brain development
Gestational Diabetes
HAPO

(Hyperglycaemia and adverse pregnancy outcomes)

Metzger et al, NEJM 2008

Multinational / cultural / ethnic study over 7 years

Large, prospective, observational, blinded study  \( n=23,316 \)

Plasma glucose \( \leq 5.8 \text{mmol/L} \) fasting and \( \leq 11.1 \text{mmol/L} \) 2 hours post 75g OGTT

Primary outcomes:

• Birth weight >90\(^{th}\) centile for GA
• Primary c-section
• Neonatal hypoglycaemia
• Cord blood c-peptide >90\(^{th}\) centile
HAPO

• Calculated OR for adverse pregnancy outcomes associated with an increase in:
  • Increase Fasting glucose of 1 SD (0.4mmol/l)
  • Increase 1 Hour glucose of 1 SD (1.7mmol/l)
  • Increase 2 hour glucose of 1 SD (1.3mmol/l)

<table>
<thead>
<tr>
<th>Glucose categories</th>
<th>Fasting Glucose (mmol/l)</th>
<th>1 Hour glucose (mmol/l)</th>
<th>2 Hour glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;4.2</td>
<td>&lt;5.8</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>2</td>
<td>4.2-4.4</td>
<td>5.9-7.3</td>
<td>5.1-6.0</td>
</tr>
<tr>
<td>3</td>
<td>4.5-4.9</td>
<td>7.4-8.6</td>
<td>6.1-6.9</td>
</tr>
<tr>
<td>4</td>
<td>4.8-4.9</td>
<td>8.7-9.5</td>
<td>7.0-7.7</td>
</tr>
<tr>
<td>5</td>
<td>5.0-5.2</td>
<td>9.6-10.7</td>
<td>7.8-8.7</td>
</tr>
<tr>
<td>6</td>
<td>5.3-5.5</td>
<td>10.8-11.7</td>
<td>8.8-9.8</td>
</tr>
<tr>
<td>7</td>
<td>&gt;5.6</td>
<td>&gt;11.8</td>
<td>&gt;9.9</td>
</tr>
</tbody>
</table>
Frequency of primary outcomes across the glucose categories (adjusted), *NEJM* 2008
Table 3. Adjusted Odds Ratios for Associations between Maternal Glycemia as a Continuous Variable and Primary and Secondary Perinatal Outcomes. *

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plasma Glucose Level</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
<td>At 1 Hr</td>
<td>At 2 Hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &gt;90th percentile</td>
<td>1.38 (1.32–1.44)</td>
<td>1.46 (1.39–1.53)</td>
<td>1.38 (1.32–1.44)</td>
<td></td>
</tr>
<tr>
<td>Primary cesarean section†</td>
<td>1.11 (1.06–1.15)</td>
<td>1.10 (1.06–1.15)</td>
<td>1.08 (1.03–1.12)</td>
<td></td>
</tr>
<tr>
<td>Clinical neonatal hypoglycemia</td>
<td>1.08 (0.98–1.19)‡</td>
<td>1.13 (1.03–1.26)</td>
<td>1.10 (1.00–1.12)</td>
<td></td>
</tr>
<tr>
<td>Cord-blood serum C peptide &gt;90th percentile</td>
<td>1.55 (1.47–1.64)</td>
<td>1.46 (1.38–1.54)</td>
<td>1.37 (1.30–1.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurity delivery (before 37 wk)</td>
<td>1.05 (0.99–1.11)</td>
<td>1.18 (1.12–1.25)</td>
<td>1.16 (1.10–1.23)</td>
<td></td>
</tr>
<tr>
<td>Shoulder dystocia or birth injury</td>
<td>1.18 (1.04–1.33)</td>
<td>1.23 (1.09–1.38)</td>
<td>1.22 (1.09–1.37)</td>
<td></td>
</tr>
<tr>
<td>Intensive neonatal care</td>
<td>0.99 (0.94–1.05)</td>
<td>1.07 (1.02–1.13)</td>
<td>1.09 (1.03–1.14)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1.00 (0.95–1.05)</td>
<td>1.11 (1.05–1.17)</td>
<td>1.08 (1.02–1.13)</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.21 (1.13–1.29)</td>
<td>1.28 (1.20–1.37)</td>
<td>1.28 (1.20–1.37)</td>
<td></td>
</tr>
</tbody>
</table>

* Odds ratios were for an increase in the glucose level of 1 SD [6.9 mg per deciliter (0.4 mmol per liter) for the fasting plasma glucose level, 30.9 mg per deciliter (1.7 mmol per liter) for the 1-hr plasma glucose level, and 23.5 mg per deciliter (1.3 mmol per liter) for the 2-hr plasma glucose level]. The model for preeclampsia did not include adjustment for hospitalization or mean arterial pressure, and presence or absence of family history of hypertension or prenatal urinary tract infection was included in the model for preeclampsia only. See Table 2 for other details about adjustments in each model.

† Data for women who had had a previous cesarean section were excluded.

‡ The P value for the quadratic (nonlinear) association was 0.013.
HAPO

- Strong correlation between increasing maternal glucose levels at 24-32 weeks gestation and a range of adverse maternal and fetal outcomes
- No specific plasma glucose values above which the risk of adverse pregnancy outcomes was markedly increased
- Pregnancy study groups (IADPSG), with Australasian representation formulated a new consensus guidelines for the testing and diagnosis of GDM
Gestational Diabetes

2.2 – Testing for gestational diabetes at 24 to 28 weeks gestation by using 75g OGTT (ADIPS 2013)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fasting glucose</th>
<th>1hr glucose</th>
<th>2hr glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td>≥ 5.1mmol/L</td>
<td>≥ 10.0mmol/L</td>
<td>≥ 8.5mmol/L</td>
</tr>
</tbody>
</table>
Recommendations for early GDM testing

For all pregnant women with risk factors for GDM:

• Moderate:
  • Ethnicity: Asian, Indian subcontinental, Aboriginal, Torres Straight Islander, Pacific Islander, Maori, Middle Eastern, non-white African
  • BMI 25-35kg/m

• High:
  • Previous GDM
  • Previously elevated BSL
  • Maternal age >40
  • Family history of GDM
  • BMI >35
  • Previous macrosomia
  • Polycystic ovarian syndrome
  • Medications: corticosteroids/antipsychotics
Gestational Diabetes

2.3 Management of elevated blood glucose

1. Target blood glucose levels close to normal with diet + ≥ 30minutes moderate exercise

   If hyperglycaemia persists:

2. Blood glucose-lowering pharmacological therapy
Gestational Diabetes

2.4 Postpartum care in GDM patients

1. Fasting glucose measured for 24 to 72 hours after delivery to ensure resolution of hyperglycaemia,
   then:

2. 2hr 75g OGTT at 6-12 weeks after delivery to rule out pre-diabetes or diabetes
Glucose monitoring and glycaemic targets
Glucose monitoring and glycaemic targets

3.1 – Self monitoring of blood glucose in pregnant women with gestational diabetes mellitus

Post meals = 1 or 2 hours after

Fasting → Post breakfast → Pre lunch → Post lunch → Pre dinner → Post dinner → Bedtime
Glucose monitoring and glycaemic targets

3.2 – Glycaemic targets in overt or GDM (ADIPS 2013)

<table>
<thead>
<tr>
<th>Time</th>
<th>Target Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial</td>
<td>$\leq 5.0\text{mmol/L}$</td>
</tr>
<tr>
<td>1 hour after start of meal</td>
<td>$\leq 7.4\text{mmol/L}$</td>
</tr>
<tr>
<td>2 hours after start of meal</td>
<td>$\leq 6.7\text{mmol/L}$</td>
</tr>
</tbody>
</table>
Blood glucose-lowering pharmacological therapy during pregnancy
Blood glucose-lowering pharmacological therapy during pregnancy

5.1 – Long acting insulin analog glargine/detemir may be initiated during pregnancy if:

• Woman needs basal insulin
• NPH has resulted in / may result in hypoglycaemia

*continue insulin detemir or insulin glargine if patient successfully taking prior to conception
Blood glucose-lowering pharmacological therapy during pregnancy

5.1 – Rapid-acting insulin analogs lispro and aspart to be used in preference to regular insulin
Blood glucose-lowering pharmacological therapy during pregnancy

5.2 – Non-insulin antihyperglycaemic agents

Glibenclamide
Metformin
Blood glucose-lowering pharmacological therapy during pregnancy

5.2a – Glibenclamide

Alternative to insulin in GDM if:
• Insufficient control with one diet + exercise trial, or:
• Patient refusal of insulin

Insulin preferred if:
• GDM diagnosed <25 weeks gestation
• Fasting plasma glucose >6.1mmol/L
**Metformin - MiG study**  
(Rowan et al, NEJM 2008)

- 2002-6 Aust-NZ  n=751 GDM (n=363 on Metformin)
- GDM= F $<5.3$mmol/l and 2/3: 1hr $>10$,  
- 2hr $>8.6$, 3hr $>7.8$mmol/l
- Randomised, open treatment
- Insulin v Metformin ± Insulin

<table>
<thead>
<tr>
<th>Primary composite endpoints</th>
<th>Neonatal hypoglycemia, RDS, Phototherapy, Birth Trauma, Prematurity, 5 minute Apgar score $&lt;7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary composite endpoints</td>
<td>Maternal glycemic control, neonatal anthropomorphic measurements, maternal hypertensive complications, post prandial glucose tolerance, acceptability/tolerability of treatment</td>
</tr>
</tbody>
</table>
Table 2. Primary Outcome and Additional Neonatal Complications.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin Group (N=363)</th>
<th>Insulin Group (N=370)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>116 (32.0)</td>
<td>119 (32.2)</td>
<td>0.99 (0.80–1.23)</td>
<td>0.95</td>
</tr>
<tr>
<td>Recurrent blood glucose level &lt;46.8 mg/dl\textsuperscript{†}</td>
<td>55 (15.2)</td>
<td>69 (18.6)</td>
<td>0.81 (0.59–1.12)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any blood glucose level &lt;28.8 mg/dl</td>
<td>12 (3.3)</td>
<td>30 (8.1)</td>
<td>0.41 (0.21–0.78)</td>
<td>0.008</td>
</tr>
<tr>
<td>Respiratory distress‡</td>
<td>12 (3.3)</td>
<td>16 (4.3)</td>
<td>0.76 (0.37–1.59)</td>
<td>0.47</td>
</tr>
<tr>
<td>Transient tachypnea</td>
<td>7 (1.9)</td>
<td>8 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>4 (1.1)</td>
<td>5 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (0.3)</td>
<td>5 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>0</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>29 (8.0)</td>
<td>31 (8.4)</td>
<td>0.95 (0.59–1.55)</td>
<td>0.85</td>
</tr>
<tr>
<td>Birth trauma\textsuperscript{§}</td>
<td>16 (4.4)</td>
<td>17 (4.6)</td>
<td>0.96 (0.49–1.87)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mild</td>
<td>16 (4.4)</td>
<td>15 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>0</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5-Min Apgar score &lt;7\textsuperscript{¶}</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>3.06 (0.32–29.26)</td>
<td>0.37</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk of gestation)</td>
<td>44 (12.1)</td>
<td>28 (7.6)</td>
<td>1.60 (1.02–2.52)</td>
<td>0.04</td>
</tr>
<tr>
<td>Iatrogenic (indicated)</td>
<td>18 (5.0)</td>
<td>13 (3.5)</td>
<td>1.41 (0.70–2.84)</td>
<td>0.33</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>26 (7.2)</td>
<td>15 (4.1)</td>
<td>1.77 (0.95–3.28)</td>
<td>0.07</td>
</tr>
<tr>
<td>Additional neonatal complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to level 2 or 3 neonatal intensive care unit</td>
<td>68 (18.7)</td>
<td>78 (21.1)</td>
<td>0.89 (0.66–1.19)</td>
<td>0.43</td>
</tr>
<tr>
<td>&gt;24-Hr stay in neonatal intensive care unit</td>
<td>46 (12.7)</td>
<td>45 (12.2)</td>
<td>1.04 (0.71–1.53)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Treatment included supplemental feeding for 129 infants (35.5\%) in the metformin group and 145 (39.2\%) in the insulin group (P=0.31), nasogastric feeding for 9 infants (2.5\%) in the metformin group and 14 (3.8\%) in the insulin group (P=0.31), and intravenous dextrose for 25 infants (6.9\%) in the metformin group and 22 (5.9\%) in the insulin group (P=0.60). Induction of labor was performed in 196 women (54.0\%) in the metformin group and 208 (56.2\%) in the insulin group (P=0.52), cesarean section in 131 women (36.1\%) in the metformin group and 142 (38.4\%) in the insulin group (P=0.33), and emergency cesarean section in 55 women (15.2\%) in the metformin group and 63 (17.0\%) in the insulin group (P=0.49). Shoulder dystocia occurred in 6 deliveries (1.7\%) in the metformin group and 11 (3.0\%) in the insulin group (P=0.33).

\textsuperscript{†} To convert values for glucose to millimoles per liter, divide by 18.

\textsuperscript{‡} Nine infants in each group were treated with continuous positive airway pressure. Five infants in the insulin group required intermittent positive-pressure ventilation (one of these infants subsequently received a diagnosis of tetralogy of Fallot).

\textsuperscript{§} Moderate or severe birth trauma included Erb’s palsy, which resolved by 6 weeks of age in one infant, and a severe brachial plexus injury in another.

\textsuperscript{¶} All these infants had 5-minute Apgar scores of 6. In the metformin group, one infant had facial bruising and one preterm infant was admitted to the neonatal intensive care unit to establish feeding. Delivery was complicated by shoulder dystocia in one infant in the insulin group, who was admitted to the neonatal intensive care unit for observation.

\textsuperscript{¶} The values are based on 94 infants in the metformin group and 101 in the insulin group.
### Table 5. Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Metformin Group (N=363)</th>
<th>Insulin Group (N=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious maternal adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection requiring hospitalization</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Antenatal</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Postnatal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Surgery†</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Antenatal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Postnatal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic arthropathy requiring opiate analgesia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other events†</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Serious fetal or neonatal adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Congenital anomalies‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Neonatal infection requiring hospitalization¶</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Other events¶</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Important maternal adverse events¶¶</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal events resulting in dose limiting</td>
<td>32 (8.8)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal events resulting in treatment cessation</td>
<td>7 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Maternal antepartum infection</td>
<td>44 (12.1)</td>
<td>38 (10.3)</td>
</tr>
</tbody>
</table>

* In the metformin group, one mother underwent surgery for cholecystectomy and one for placement of a right ureteric stent; in the insulin group, one mother had an appendectomy for appendicitis complicated by abscess.
† In the metformin group, there was one mother each with antepartum severe superficial thrombophlebitis, antepartum granulomatous mastitis, postpartum iatrogenic pulmonary edema, and postpartum anaphylactic reaction to anesthetic with stridor. In the insulin group, there were two mothers with severe preeclampsia (requiring prolonged hospitalization or care in an obstetrical intensive care unit) and one mother each with postpartum hemorrhage requiring transfusion and urinary incontinence.
‡ In the metformin group, two infants had small ventricular septal defects, three had hypospadias, one had hydrenephrosis, two had talipes equinovarus, two had a dislocatable hip, and one had a bifid thumb. In the insulin group, two infants had ventricular septal defects, one had coarctation of the aorta, one had tetralogy of Fallot, one had an atrial septal defect with a minor cleft palate, one had choanal atresia, one had a ureterocele, one had hydrometrocolpos, one had hemifacial microsomia, three had talipes equinovarus, three had preauricular skin tags, and three had a dislocatable hip.
¶ In the metformin group, one infant each had gastroenteritis, viral pneumonia, renal sepsis, and sepsis of unknown source. In the insulin group, one infant each had viral meningitis and cytomegalovirus infection.
¶¶ In the metformin group, one infant each had neonatal abstinence syndrome due to maternal use of opiates, stridor due to a short arypegiotic fold, sensorineural hearing loss (probably due to a connexin mutation), and inguinal hernia requiring repair. In the insulin group, one infant each had trisomy 13 and hypoxic encephalopathy with Erb’s palsy.

Important adverse events were those leading to dose reduction or cessation of treatment or those occurring with a frequency of at least 5%.
Summary – MiG study

Non inferiority study
Primary composite endpoint occurred in:
32% Metformin and 32.2% Insulin
RR 1.0 (95% CI 0.90-1.10)

Limitations:
• Open label design
• Lack of blinding
• Use of superiority design
• Use of composite endpoints of very different clinical parameters
• Lack of follow up of offspring
Nutrition therapy and weight gain targets
Nutrition therapy and weight gain targets

Medical nutrition therapy for all pregnant women with overt or gestational diabetes mellitus

• Carbohydrate controlled meal
• Adequate nutrition
• Appropriate weight gain
• Normoglycaemia
• Avoid ketosis
Nutrition therapy and weight gain targets

Weight gain targets for overt or GDM

<table>
<thead>
<tr>
<th>Pre-pregnancy BMI</th>
<th>Total Weight Gain</th>
<th>2\textsuperscript{nd}/3\textsuperscript{rd} Trimester weight gain rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>12.5-18kg</td>
<td>0.51kg/week</td>
</tr>
<tr>
<td>Healthy weight (18.5-25)</td>
<td>11.5-16kg</td>
<td>0.42kg/week</td>
</tr>
<tr>
<td>Overweight (25-30)</td>
<td>7-11.5kg</td>
<td>0.28kg/week</td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>5-9kg</td>
<td>0.22kg/week</td>
</tr>
</tbody>
</table>

*Assuming 0.5-2kg weight gain in first trimester*
Nutrition therapy and weight gain targets

Obese women with overt or GDM should reduce calorie intake:

Moderate calorie restriction
(1600-1800kcal/day, ~30% reduction)
Nutrition therapy and weight gain targets

Limit carbohydrate intake to 35-45% of total calories

• 3 small to moderate sized meals

• 2-4 snacks including evening snacks

• Minimum of 175g/day of carbohydrates
Nutrition therapy and weight gain targets

Same mineral / vitamin intake guidelines as for non diabetics, except folate:

1. Folic acid 5mg/day beginning 3 months preconception
2. Folic acid dose reduced to 0.4-1mg/day in second trimester
3. Folic acid to be continued until breastfeeding completion

Endocrine Society guidelines 2013
J Obstet Gynaecol Can, 2007
Labour, delivery, lactation and postpartum care
Labour, delivery, lactation, and postpartum care

Blood glucose targets during labour / delivery:

4.0 – 7.0 mmol/L

- Neonatal hypoglycaemia
- Fetal distress
- Birth asphyxia
- Abnormal fetal heart rate

Endocrine Society guidelines 2013
Labour, delivery, lactation, and postpartum care

Lactation

Breastfeed infant whenever possible

- ↓ Childhood obesity
- ↓ Impaired glucose tolerance and diabetes in mother/child
- Helps postpartum weight loss in mother

Am J Clin Nutr, 2006
Ir Med J, 2012
Labour, delivery, lactation, and postpartum care

Lactation

Continue glibenclamide / metformin during breastfeeding if needed

• Metformin: low concentration in breast milk
• Glibenclamide: no detected in breast milk

Expert Opin Drug Saf, 2007
J Pediatr, 2006
Labour, delivery, lactation, and postpartum care

Postpartum contraception

No effect of GDM on choice of contraception
Gestational Diabetes

Postpartum care in GDM patients

1. GDM patients:
   • 30% risk of recurrence of GDM in subsequent pregnancies
   • 50% risk of developing type 2 diabetes within 10-20 years

Recommendation: 2hr 75g OGTT at 6-12 weeks after delivery to rule out pre-diabetes or diabetes, and then annually
Labour, delivery, lactation, and postpartum care

Screening for postpartum thyroiditis in T1DM

TSH at 3 months and 6 months
Summary
Summary

Preconception care of women with diabetes

• Counsel, assess retinas, kidneys and thyroid, screen for vascular risk factors and optimise weight

• Optimise blood glucose and blood pressure in advance

• Commence supplemental folic acid 3 months prior to conception

• Discontinue / avoid ACE inhibitors, ARBs, anti-dyslipidaemias (consider alternatives)
Summary

Gestational diabetes

- Screening moderate-high risk pregnant patients at first visit for GDM
- Test for GDM at 24-28 weeks by 2 hours 75g OGTT
- Manage hyperglycaemia initially by lifestyle therapy, then pharmacological therapy if unsuccessful
- Rule out diabetes with 2 hour 75g OGTT at 6-12 weeks
- Counsel GDM patients to reduce risk of future DM
Summary

Glucose monitoring and glycaemic targets

• Achieve glucose targets
  • Preprandial ≤5.0mmol/L
  • 1 hour postprandial ≤7.4mmol/L
  • 2 hours postprandial ≤6.7mmol/L
Summary

Nutrition therapy and weight gain targets

• Medical nutrition therapy for all pregnant with GDM
• Achieve weight gain targets dependent on BMI
• Moderate calorie intake reduction in obese, limiting carbohydrates
• Folic acid to continue from three months until completion of breastfeeding
• Intake of minerals and vitamins like other non-diabetic pregnant
Summary

Blood glucose-lowering pharmacological therapy

- Long acting insulin analog glargine/detemir better than NPH but more expensive
- Rapid acting insulin analog (lispro & aspart) better than regular insulin
- Multiple daily dose insulin preferred for initiation during pregnancy
- Glibenclamide/Metformin good alternative to insulin in GDM
Summary

Labour, delivery, lactation, postpartum care

- Blood glucose to be maintained between 4 – 7mmol/L during labour and delivery
- Breastfeeding should be done by all women, even if patient on metformin or glibenclamide
- Screen type 1 diabetics for postpartum thyroiditis
A 25 year old woman with a 5-year history of type 1 diabetes advises you she would like to try to conceive as soon as possible. Her HbA1c is 8.5%

What advice should you give her?

a) She can safely proceed with trying to conceive
b) She should defer trying to conceive until her HbA1c <6%
c) She should defer trying to conceive until her HbA1c is as close to normal as possible when this can be safely achieved
d) She should begin using continuous glucose monitoring
A 29 year old woman with type 1 diabetes and hypertension is newly pregnant. She has known stable retinopathy. Her HbA1c is 6.5%. Her blood pressure is 120/85mmHg.

What advice would you give her regarding her retinopathy?

a) Tell her that her retinopathy can worsen during pregnancy and arrange for regular eye exams during the pregnancy
b) Tell her that her retinopathy is stable, it is unlikely to progress during the pregnancy

c) Advise her of the great dangers to her vision if she continues the pregnancy and recommend she terminate the pregnancy

d) Recommend she see an eye care professional in the near future then again after she has delivered
Question 3

• A 32 year old woman with type 2 diabetes being treated with metformin has just delivered a healthy infant at term. She will be breastfeeding the baby.

• What should you recommend for this woman?
  a) She should discontinue the metformin and take insulin instead
  b) She should continue the metformin
  c) She should not breastfeed the infant
  d) She should discontinue the metformin and take glibenclamide instead
Thank you