Gestational Diabetes and Type 2 Diabetes in Pregnancy

Rochan Agha-Jaffar
Diabetes & Endocrinology Consultant
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Number of Live Births affected by Hyperglycaemia in 1,000s: IDF Atlas (2017)

- < 100,000
- 100,000 – 500,000
- 500,000 – 1,000,000
- 1,000,000 – 2.5 million
- 2.5 – 5 million
- > 5 million
- No data
UK Data: 177 800 pregnancies complicated by hyperglycaemia

- Gestational Diabetes: 87.5%
- Type 1 Diabetes: 7.5%
- Type 2 Diabetes: 5.0%

"Hyperglycaemia first detected at any time during pregnancy"\(^1\)

\(^1\) Diabetes in pregnancy. Clinical Guideline. NICE 2008
Objectives

• Risks associated with development of hyperglycaemia in pregnancy
• Methods for mitigating materno-fetal risk
• Review materno-fetal outcomes in T2DM
• Understand the long-term risks of diabetes in pregnancy for mother and baby
• Long-term effects of in-utero exposure to metformin
Effects of Exposure to in Utero Hyperglycaemia

- First Trimester: Congenital Anomalies
- Second Trimester: Excess fetal growth
- Third Trimester: Metabolic imprinting
- Postnatal period: Physiological, Metabolic

12 weeks → 40 weeks
Early Fetal development

• Risk congenital malformations 3-5 times higher than background population

• Teratogenic effects of hyperglycaemia and ketonaemia implicated in fetal embryopathy

• “Oxidative stress hypothesis”
Pathophysiology Fetal Macrosomia

Pre-pregnancy determinants
insulin resistance

- Ethnicity
- Physical inactivity
- Obesity
- Dietary composition
- Polycystic ovarian syndrome/hypertension

Insulin resistance
- Tumour necrosis factor-α
- Placental lactogen
- Placental growth hormone
- Oestrogen
- Progesterone
- Cortisol

Increased glucose levels

Mother
- Persistent hyperglycaemia
- Defective insulin secretion

Placenta
- Glucose flux
- Hydrolysis to free fatty acids
- Placental hormone production

Fetus
- Pancreatic production of insulin
- Substrates for fetal growth
- Enhanced fetal growth

Nature Reviews Endocrinology (12): 533-546
Postnatal Complications
Intrauterine Death/ Still Birth

3-5 times higher than background rate

Mechanisms poorly understood

Thought to relate
• fetal hypoxia
• Placental insufficiency

Teramo et al 2004 Diabetologia
Objectives

• Risks associated with development of hyperglycaemia in pregnancy

• **Methods for mitigating materno-fetal risk**

• Review materno-fetal outcomes in T2DM

• Understand the long-term risks of diabetes in pregnancy for mother and baby

• Long-term effects of in-utero exposure to metformin
Type 2 Diabetes: Preconception Care

- Well established guidance for women with pre-gestational diabetes
- Evidence base largely exists in women with previous neonate with neural tube defect
- Consider potential vitamin B12 deficiency
Type 2 Diabetes: Preconception Care

- **Statins** – potentially teratogenic
  - Congenital malformation risk Unadjusted RR 1.79 (95% CI 1.43-2.27): Adjusted RR 1.07 (95% CI 0.85-1.37)

- **ACE/ARBs** – unclear effects of first trimester exposure
  - Use in 2\(^{\text{nd}}\)/3\(^{\text{rd}}\) trimester contraindicated due to damaging effects on kidneys
Type 2 Diabetes: Preconception Care

Target HbA1c $\leq 48$ mmol/mol
Type 2 Diabetes Antenatal Considerations: Pre-eclampsia Prevention

- N=1776

- High risk for pre-term PET

- Randomised 150mg aspirin versus placebo from 12 weeks gestation

- NOT specifically diabetes

Rolnik et al 2017 NEJM 377:613
Antenatal Care: Further Considerations

Retinal screening recommended at least twice (booking and 28 weeks)

Risk progression retinopathy not as high as Type 1 diabetes - occurred in 14%

Reduction in HbA1c from baseline to 34 weeks significantly higher in those with progression

Glucose Monitoring in Type 2/ GDM

- FPG < 5.5 mmol/L
- One hour Post-prandial glucose < 7.8 mmol/L

- HbA1c monitoring should be used second line
- No evidence base for use continuous glucose monitoring in Type 2 Diabetes/ GDM
Fetal Monitoring
RCT metformin vs insulin in 751 women with GDM
- Trial designed to rule out 33% increase in composite of the following
  - Neonatal hypoglycaemia/ RDS/ need for phototherapy/ birth trauma/ APGAR <7/ prematurity
- Improved satisfaction in women receiving metformin
- 46.3% required supplemental insulin
Metformin versus Insulin for the Treatment of Gestational Diabetes

<table>
<thead>
<tr>
<th>Table 2. Primary Outcome and Additional Neonatal Complications.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>Primary composite outcome</td>
</tr>
<tr>
<td>Recurrent blood glucose level &lt;46.8 mg/dl†</td>
</tr>
<tr>
<td>Any blood glucose level &lt;28.8 mg/dl</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight change — kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss from enrollment to postpartum visit ¶¶¶</td>
</tr>
<tr>
<td>Gain from early pregnancy to enrollment</td>
</tr>
<tr>
<td>Gain from enrollment to 36 or 37 wk of gestation****</td>
</tr>
</tbody>
</table>

Metformin versus insulin for treatment of Gestational Diabetes. NEJM 2008(358)
Metformin in Gestational Diabetes: the offspring follow-up (MiG TOFU). DC. 2011(34)
Timing of Delivery

- Emergency caesarian section
- NICU
- Hypoglycaemia
- RDS
- Steroids
- Stillbirth
- Shoulder dystocia

Gestational age: 39 40
Objectives

- Risks associated with development of hyperglycaemia in pregnancy
- Methods for mitigating materno-fetal risk
- **Review materno-fetal outcomes in T2DM**
- Understand the long-term risks of diabetes in pregnancy for mother and baby
- Long-term effects of in-utero exposure to metformin
NICE Guideline:
- Keep HbA$_{1c}$ <48 mmol/mol where achievable without causing problematic hypoglycaemia
- Use a folic acid supplement prior to pregnancy
- Suspend use of statins and ACE inhibitors/ARBs

Only one in twelve women (8 per cent) were well prepared for pregnancy

Adverse Pregnancy Outcomes

Key Finding:
Stillbirth rate

Stillbirth rates were more than twice, and neonatal death rates nearly four times the general population rate.

Key Finding:
HbA$_{1c}$

Higher first trimester HbA$_{1c}$ was related to congenital anomaly rates and in women with Type 1 diabetes to stillbirth and neonatal death.
Perinatal Outcomes in T2DM

• East Anglia Study Group for Improving Pregnancy Outcomes in women with Diabetes (EASIPOD)
• 682 consecutive T1DM and T2DM (2006-2009)
  – 59.8% T1DM: 40.2% T2DM
  – HbA1c: 63mmol/mol T1DM vs 52 mmol/mol T2DM
  – No difference combined congenital anomaly and perinatal mortality rates 67/1000 T1DM vs 50/1000 T2DM

Hewapathirana NM, Murphy HR Current Diabetes Reports 2014
Further Challenges Associated with T2DM

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age(^a) (years)</td>
<td>30.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Median duration(^b) of diabetes (years)</td>
<td>14.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Median Body Mass Index (kg/m(^2))</td>
<td>26.1</td>
<td>32.6</td>
</tr>
</tbody>
</table>

- \(^a\) Age at completion of pregnancy.
- \(^b\) Duration of diabetes at start of pregnancy.

Non-white ethnicity: 59.4% versus 23% T1DM

Social deprivation quintile 5: 41.5% versus 24.0% T1DM
Stillbirth Rates, England and Wales: 1927 to 2018

Stillbirths per 1,000 live births and stillbirths
Still Birth Rates

- UK has one of the highest still birth rates in high income studies
- Overall rate 4.7 per 1000 births
HbA1c measured at 47 days in 16,122 women: New Zealand 2008-2010

HbA1c assessed against OGTT <20 wks

Women invited for OGTT if HbA1c >5.6%
Table 2—Pregnancy outcomes stratified according to HbA1c measurement at ≤20 weeks’ (140 days’) gestation, excluding women treated for GDM

<table>
<thead>
<tr>
<th></th>
<th>HbA1c 5.9–6.4% (41–46 mmol/mol)</th>
<th>HbA1c &lt; 5.9% (&lt;41 mmol/mol)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 200</td>
<td>n = 7,987</td>
<td></td>
</tr>
<tr>
<td>Delivery gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>16 (8.0)</td>
<td>392 (4.9)</td>
<td>1.66 (1.01–2.74)*</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>3 (1.5)</td>
<td>71 (0.9)</td>
<td>1.67 (0.55–5.10)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>35 (17.5)</td>
<td>1,016 (12.7)</td>
<td>1.44 (1.01–2.06)*</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65 (32.5)</td>
<td>2,428 (30.4)</td>
<td>1.10 (0.82–1.47)</td>
</tr>
<tr>
<td>Emergency</td>
<td>33 (16.5)</td>
<td>1,529 (19.1)</td>
<td>0.84 (0.58–1.21)</td>
</tr>
<tr>
<td>Major congenital anomalies</td>
<td>n = 7,992</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (3.5)</td>
<td>103 (1.3)</td>
<td>2.67 (1.28–5.53)*</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>11 (5.5)</td>
<td>181 (2.3)</td>
<td>2.42 (1.34–4.38)*</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>4 (2.0)</td>
<td>38 (0.5)</td>
<td>3.96 (1.54–10.16)*</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>5 (2.5)</td>
<td>79 (1.0)</td>
<td>2.47 (1.05–5.85)*</td>
</tr>
<tr>
<td>Birth weight</td>
<td>n = 199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3,480.2 (597.0)</td>
<td>3,483.8 (571.0)</td>
<td>P = 0.93</td>
</tr>
<tr>
<td>&gt;4,000 g</td>
<td>34 (17.1)</td>
<td>1,240 (15.5)</td>
<td>1.12 (0.78–1.61)</td>
</tr>
<tr>
<td>Population birth weight centiles†</td>
<td>n = 199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>22 (11.1)</td>
<td>1,202 (15.1)</td>
<td>0.71 (0.46–1.10)</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>26 (13.1)</td>
<td>655 (8.2)</td>
<td>1.66 (1.11–2.48)*</td>
</tr>
<tr>
<td>Customized birth weight centiles‡</td>
<td>n = 199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>23 (11.6)</td>
<td>1,173 (14.7)</td>
<td>0.76 (0.50–1.17)</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>21 (10.1)</td>
<td>641 (8.0)</td>
<td>1.34 (0.86–2.09)</td>
</tr>
</tbody>
</table>
Hyperglycemia recognised in early pregnancy is phenotypically type 2 diabetes mellitus not gestational diabetes mellitus: a case control study

- Case control study (n=200)
- Women with hyperglycaemia diagnosed early in pregnancy (eGDM n=40) compared to two separate weight and age-matched control groups
  - Recognised Type 2 diabetes (T2DM, n=80)
  - GDM (rtGDM, n=80)
Maternal baseline demographics and biochemical data

<table>
<thead>
<tr>
<th>Metric</th>
<th>eGDM (n = 40)</th>
<th>T2DM (n = 80)</th>
<th>rtGDM (n = 80)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Age (years)</td>
<td>33.9 (±4.5)</td>
<td>34.2 (±5.1)</td>
<td>33.7 (±5.5)</td>
<td>.35</td>
</tr>
<tr>
<td>Mean (SD) Height (cm)</td>
<td>161.7 (±7.3)</td>
<td>161.5 (±7.2)</td>
<td>160.8 (±6.0)</td>
<td>.79</td>
</tr>
<tr>
<td>Mean (SD) Weight (kg)</td>
<td>83.6 (±15.8)</td>
<td>84.1 (±19.2)</td>
<td>78.8 (±12.5)</td>
<td>.14</td>
</tr>
<tr>
<td>Median (IQR) BMI (kg/m²)</td>
<td>32.0 (27.0–35.0)</td>
<td>31.0 (28.0–35.9)</td>
<td>30.4 (27.9–33.9)</td>
<td>.50</td>
</tr>
<tr>
<td>Non-White ethnicity % (n)</td>
<td>80.0 (32)</td>
<td>86.2 (69)</td>
<td>76.3 (61)</td>
<td>.27</td>
</tr>
<tr>
<td>Black African–Caribbean</td>
<td>25.0 (10)</td>
<td>26.2 (21)</td>
<td>22.5 (18)</td>
<td></td>
</tr>
<tr>
<td>Arab/North African</td>
<td>20.0 (8)</td>
<td>15.0 (12)</td>
<td>7.5 (6)</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>25.0 (10)</td>
<td>37.5 (30)</td>
<td>18.8 (15)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10.0 (4)</td>
<td>7.5 (6)</td>
<td>27.5 (22)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Primigravida % (n)</td>
<td>17.5 (7)</td>
<td>18 (22.5)</td>
<td>37 (46.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multiparous % (n)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.0 (10)</td>
<td>11 (13.8)</td>
<td>4 (5.0)</td>
<td></td>
</tr>
<tr>
<td>History previous pregnancy complicated by GDM % (n)</td>
<td>71.8 (28)</td>
<td>38.5 (30)</td>
<td>0.0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>20.0</td>
<td>23.4</td>
<td>3.8</td>
<td>.01</td>
</tr>
<tr>
<td>Hypertension % (n)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(8)</td>
<td>(18)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) HbA1c (%)</td>
<td>6.4 (6.1–7.3)</td>
<td>6.8 (6.1–7.8)</td>
<td>5.6 (5.3–5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR) HbA1c (mmol/mol)</td>
<td>46 (43–56)</td>
<td>51 (43–62)</td>
<td>38 (34–40)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Variations in Fetal Birth Weight and Adjusted Birth Weight Centile

- eGDM (n=36)
- T2DM (n=77)
- rGDM (n=79)
Postpartum Glucose Assessments

Footnotes: ** Denotes significance level < 0.05.

Abbreviations: eGDM women diagnosed with hyperglycaemia < 20 weeks gestation, rtGDM women diagnosed with gestational diabetes 24-28 weeks gestation, FPG Fasting plasma glucose, IGT Impaired glucose tolerance, T2DM Type 2 diabetes mellitus.
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- Long-term effects of in-utero exposure to metformin
Long Term Risks for the Mother

Kim et al Diabetes Care 2002
Effects of Exposure to in Utero Hyperglycaemia

- **First Trimester**: Congenital Anomalies
- **Second Trimester**: Excess fetal growth
- **Third Trimester**: Metabolic imprinting
- **Postpartum**: Physiological, Metabolic

Long term impact

- **12 weeks**
- **40 weeks**
Maternal Hyperglycaemia and Childhood Obesity

Prevalence (%)

- Weight > 85th centile
- Weight > 95th centile

Graph showing the prevalence of different glucose levels and weight percentiles.

+ GCT, Normal OGTT
Normal Fasting Glucose
Fasting > 5.3mmol/L

Childhood Obesity and Metabolic Imprinting: the ongoing effects of childhood obesity.
Diabetes Care. 2007; 30 (9): 2287-2292
Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark


• Follow up offspring born to women in one of three groups: GDM, T1DM, background population

• Pre-diabetes/ diabetes was present in 21%, 11% and 4% offspring aged 18-27 years respectively

• 8-fold and 4-fold increase in prediabetes/ diabetes risk in GDM and T1DM offspring
Mild Gestational Diabetes Mellitus and Long-Term Child Health


• Follow up study of children enrolled in an RCT of “mild GDM” treatment versus no treatment (n=500)

• Maternal demographics similar in two groups

• BMI ≥95th and ≥85th percentiles similar in treated versus non-treated groups: 20.8% vs. 22.9% and 32.6% versus 38.6% respectively

• No difference in metabolic dysfunction
Objectives

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• Long-term effects of in-utero exposure to metformin
Meta-analysis of nineteen studies (3723 neonates)

Neonates born to metformin treated mothers had

- Lower birth weights (mean difference -107.7g)
- Lower OR macrosomia and LGA (OR 0.59 and 0.78 respectively) relative to insulin treated mothers
- Significantly higher BMI in metformin treated group
<table>
<thead>
<tr>
<th>Adiposity index</th>
<th>Study details</th>
<th>Mean difference (fixed)</th>
<th>95% CI</th>
<th>Significance</th>
<th>Heterogeneity test</th>
</tr>
</thead>
</table>
| Total fat mass (DEXA)                | Adelaide (n = 61)        | 0.20                    | -0.11, 0.51         | *p = 0.25*   | *p = 0.15, I^2 = 52%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Abdominal fat mass (DEXA)            | Adelaide (n = 61)        | 79.80                   | -59.32, 218.92      | *p = 0.26*   | *p = 0.11, I^2 = 60%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Abdominal fat volume (MRI)           | Adelaide (n = 12)        | 0.44                    | 0.06, 0.82          | *p = 0.02*   | *p = 0.84, I^2 = 0%*
|                                      | Auckland (n = 92)        |                         |                     |              |                    |
| Abdominal subcutaneous fat volume (MRI)| Adelaide (n = 12)     | 0.29                    | -0.07, 0.65         | *p = 0.11*   | *p = 0.95, I^2 = 0%*
|                                      | Auckland (n = 92)        |                         |                     |              |                    |
| Visceral fat volume (MRI)            | Adelaide (n = 12)        | 0.41                    | 0.05, 0.77          | *p = 0.03*   | *p = 0.85, I^2 = 0%*
|                                      | Auckland (n = 92)        |                         |                     |              |                    |
| Thigh fat mass (DEXA)                | Adelaide (n = 61)        | 90.77                   | -148.68, 330.23     | *p = 0.46*   | *p = 0.46, I^2 = 61%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Arm fat mass (DEXA)                  | Adelaide (n = 61)        | 102.57                  | -73.34, 278.47      | *p = 0.25*   | *p = 0.09, I^2 = 65%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Bicep skinfold thickness             | Adelaide (n = 109)       | 0.53                    | -0.60, 1.66         | *p = 0.35*   | *p = 0.21, I^2 = 36%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Tricep skinfold thickness            | Adelaide (n = 109)       | 0.64                    | -0.76, 2.04         | *p = 0.83*   | *p = 0.37, I^2 = 70%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
| Subscapular skinfold thickness       | Adelaide (n = 109)       | 1.05                    | -0.70, 2.79         | *p = 0.24*   | *p = 0.32, I^2 = 0%*
|                                      | Auckland (n = 98)        |                         |                     |              |                    |
Strategies to Prevent GDM

Dietary intervention
- Results conflicting

Increased physical activity
- No benefit with intervention

Combined lifestyle interventions
- Improved materno-fetal outcomes in absence of improving maternal hyperglycaemia
Thank you!

Rochan Agha-Jaffar
r.agha-jaffar@imperial.ac.uk