PREGNANCY: THE KIDNEY MARATHON
A training guide for women with diabetes

Katherine Clark
Dr Kate Bramham
Preparation for the marathon
Running the Marathon
Finishing the marathon
Diabetic nephropathy and pregnancy – the perfect storm

- Vascular Disease
- Poor placentation
- Nephropathy
- Glycaemic Control
- Retinopathy
Getting pregnant
Diabetes often has no effect on fertility

Type 1 diabetes
• No reduction in fertility
• Increased menstrual irregularity
• Delayed menarche
• Premature menopause

Type 2 diabetes
• Association with polycystic ovaries
The proportion of type 2 diabetes is increasing in pregnancy

### 2002-3

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>30.0</td>
</tr>
<tr>
<td>Median duration of diabetes (years)</td>
<td>13.0</td>
</tr>
<tr>
<td>Median BMI (kg/m²)</td>
<td>26.0</td>
</tr>
</tbody>
</table>

### 2016-17

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
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</tr>
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<tr>
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</tr>
<tr>
<td>Median BMI (kg/m²)</td>
<td>26.0</td>
</tr>
</tbody>
</table>
Incidence of nephropathy in pregnant women with pre-existing diabetes is falling

Klemetti et al Diabetologica 2015

N=3808 pregnancies

Confidential Enquiry Maternal and Child Health 2007
**Pregnancy outcome is optimised pre-conception**

Pre-conception counselling is recommended for **ALL** women with type 1 and type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Pre-existing diabetes</th>
<th>General maternity population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned Pregnancy</td>
<td>158/384 (41%)</td>
<td>58%</td>
</tr>
<tr>
<td>Use of contraception in 12mths before pregnancy</td>
<td>107/392 (27%)</td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy folic acid</td>
<td>102/380 (27%)</td>
<td>&lt;10-50%</td>
</tr>
<tr>
<td>Smoking</td>
<td>107/386 (28%)</td>
<td>35%</td>
</tr>
</tbody>
</table>

*Confidential Enquiry into Maternal and Child Health 2007*
Preparation for the marathon
Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)
Every 1% rise in pre-conception HbA1c over 6.3% associated with 30% increased odds of birth defects

Pre-existing nephropathy confers additional risk
OR 2.45 (1.14-5.25)

Bell et al Diabetologia 2012
Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

**Aim:** HbA1c <6.5%
Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

**Aim**: HbA1c <6.5%

Max RAAS blockade
Treat hypertension
Folic Acid
ACE Inhibitors / ARBs should not be used in pregnancy

| Ramipril, Lisinopril, Fosinopril, Enalapril, Quinapril, Perindopril, Trandolapril, Benazepr | Candesartan, Irbesartan, Olmesartan, Losartan, Diovan, Valsartan, Telmisartan, Eprosartan |

‘Avoid teratogenic medications in sexually active women of child-bearing potential’

‘Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists should be discontinued before conception or as soon as pregnancy is confirmed.’

‘Women with diabetic nephropathy continue angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive’
First trimester ACEI exposure is considered teratogenic BUT…

Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study

1995 – 2008
Northern California

De-Kun Li principal investigator¹, Chunmei Yang program analyst¹, Susan Andrade research associate professor², Venessa Tavares program analyst¹, Jeannette R Ferber program analyst¹

Risk of congenital heart defects:

<table>
<thead>
<tr>
<th></th>
<th>ACEi v Controls</th>
<th>Other anti-HT v Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of defects</td>
<td>3.9% v 1.6%</td>
<td>2.4% v 1.6%</td>
</tr>
<tr>
<td>OR</td>
<td>1.54 (95% CI 0.90 to 2.62)</td>
<td>1.52 (95% CI 1.04 to 2.21). P&lt;0.05</td>
</tr>
</tbody>
</table>

Hypertension is associated with risk of congenital abnormalities
NOT ACEI
First trimester ACEI exposure is considered teratogenic BUT…

1,333,624 pregnancies
4,107 (0.31%) exposed to ACE inhibitors

<table>
<thead>
<tr>
<th>Congenital Malformations</th>
<th>Exposed (n=4,107)</th>
<th>Unexposed (n=1,329,517)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>244 (5.94)</td>
<td>43,323 (3.26)</td>
<td>1.82 (1.61–2.06)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>139 (3.38)</td>
<td>15,272 (1.15)</td>
<td>2.95 (2.50–3.47)</td>
</tr>
<tr>
<td>CNS</td>
<td>11 (0.27)</td>
<td>2,433 (0.18)</td>
<td>1.46 (0.81–2.64)</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; CNS, central nervous system.
Data are n (%) unless otherwise specified.
* Cell size less than 11, which cannot be disclosed in accordance with the data use agreement.
... the increased risk appears to be attributable to the underlying condition NOT exposure

<table>
<thead>
<tr>
<th>Risk</th>
<th>Exposed (n=2,631)</th>
<th>Unexposed (n=15,884)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>142 (5.40)</td>
<td>142 (5.40)</td>
<td>634 (3.99)</td>
<td>1.35 (1.13–1.61)</td>
</tr>
<tr>
<td>77 (2.93)</td>
<td>77 (2.93)</td>
<td>260 (1.64)</td>
<td>1.79 (1.39–2.30)</td>
</tr>
<tr>
<td>*</td>
<td>45 (0.28)</td>
<td>45 (0.28)</td>
<td>1.07 (0.51–2.27)</td>
</tr>
</tbody>
</table>
Continuing RAAS blockade pre-conception in women with diabetic nephropathy

8 women (Cr 0.8±0.05mg/dl)

>6 months until proteinuria <500mg

Intensive RAAS blockade
  (Captopril – 37.5-75mg daily)

• Pre-ACEI Proteinuria 1633±66mg/24hrs
• Post-ACEI Proteinuria 273±146mg/24hrs

Improved glycaemic control pre-pregnancy

Hod et al NDT 1995
Continuing RAAS blockade pre-conception in women with diabetic nephropathy

Only 2 women had proteinuria >1000mg during pregnancy (1903mg / 3578mg/24hr)

Hod et al NDT 1995
Does pre-pregnancy RAAS blockade improve outcomes?

<table>
<thead>
<tr>
<th>Antihypertensive Therapy Strategy</th>
<th>Ekbom et al., 2001 (25)</th>
<th>Nielsen et al., 2006 (54)</th>
<th>Nielsen et al., 2009 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Eclampsia</td>
<td>BP &gt;140/90 mmHg</td>
<td>BP &gt;135/85 mmHg</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP &gt;95 mmHg</td>
<td>UAE &gt;2 g/24 h</td>
<td>UAE ≥300/24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACE Inhibitor before</td>
<td>ACE Inhibitor before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Number</td>
<td>26</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>49±5, 10±8</td>
<td>6.8±0.5, 7.3±1.5</td>
<td></td>
</tr>
<tr>
<td>HbA1c at inclusion (%)</td>
<td>8.1±0.9, 6.8±0.5</td>
<td>7.3±1.5, 7.3±1.5</td>
<td></td>
</tr>
<tr>
<td>Week of onset of antihypertensive therapy</td>
<td>29 (20–34)</td>
<td>13 (Before-34)</td>
<td>Before (Before-14)</td>
</tr>
<tr>
<td>Patients on antihypertensive therapy during pregnancy</td>
<td>9 (35)</td>
<td>10 (50)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>ACE inhibitor before pregnancy</td>
<td>5 (19)</td>
<td>9 (45)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Systolic BP at inclusion (mmHg)</td>
<td>121±13</td>
<td>121±14</td>
<td>117±14</td>
</tr>
<tr>
<td>Diastolic BP at inclusion (mmHg)</td>
<td>71±8</td>
<td>73±8</td>
<td>74±8</td>
</tr>
<tr>
<td>UAE (mg/24 h)</td>
<td>69 (16–78)</td>
<td>74 (30–287)</td>
<td>91 (30–198)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>11 (42)</td>
<td>4 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Preterm delivery before 34 wk</td>
<td>6 (23)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Preterm delivery before 37 wk</td>
<td>16 (62)</td>
<td>8 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3124±767</td>
<td>3279±663</td>
<td>3471±670</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major congenital malformations</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
We definitely need to ensure early detection of pregnancy

Recommend continue Angiogensin Converting Enzyme Inhibitors until conception

Test frequently for pregnancy
Avoid pregnancy if >86mmol/mol (10%)

**Aim:** HbA1c <6.5%

Max RAAS blockade
Treat hypertension
Folic Acid
Regular pregnancy testing

If BMI >27kg/m²:
Dietary review
Weight loss
Avoid pregnancy if >86mmol/mol (10%)

**Aim:** HbA1c <6.5%

Max RAAS blockade

Treat hypertension

Folic Acid

Regular pregnancy testing

If BMI >27kg/m²:

Dietary review

Weight loss
Things to do when you see a positive pregnancy test

I'M PREGNANT!

Involve the MDT

Retinal assessment if non within 3 months

Confirmation of viability and gestational age <9 weeks

HbA1c to assess risk

Review medications

Advice regarding nausea and vomiting and glucose control

Start aspirin 75mg OD

Start vitamin D
Over the start line: What’s needed now?!
Antenatal care

Multi-disciplinary Care:
- Midwives
- Obstetricians
- Diabetologist
- Nephrologist
- Nurses
- Dieticians
- Ophthalmologists...
Continuity of appropriate carers must be a primary aim

“Continuity of carer is even more important particularly for women with pre-existing health… conditions who are being cared for by multidisciplinary team maternity professionals.”

RCM (2019)

‘The right people with the right skills at the right time’

Sandall (2011)

‘Intuitive knowledge’

Berg, (2005)
Multi-disciplinary Care:
Midwives
Obstetricians
Diabetologist
Nephrologist
Nurses
Dieticians
Ophthalmologists
...

Control
blood sugar

Antenatal care – running the marathon!
Glycaemic control during normal pregnancy is challenging.
# Safety of Medications in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>Human Teratogenicity</th>
<th>Fetal/neonatal effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isophane (NHP) insulin</td>
<td>B</td>
<td>×</td>
<td>×</td>
<td>First choice long acting insulin</td>
</tr>
<tr>
<td>Rapid-acting insulin analogues e.g. aspart, lispro</td>
<td>B</td>
<td>×</td>
<td>×</td>
<td>May be preferable to start pre-pregnancy</td>
</tr>
<tr>
<td>Longer-acting insulin analogues e.g. detemir, glargine</td>
<td>C</td>
<td>×</td>
<td>×</td>
<td>Increasing evidence to suggest safety</td>
</tr>
<tr>
<td>Metformin</td>
<td>B</td>
<td>×</td>
<td>×</td>
<td>GFM or Type 2 only</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>C</td>
<td>×</td>
<td>×</td>
<td>Doses &lt;20mg/day less likely to cause neonatal hypoglycaemia</td>
</tr>
<tr>
<td>Thiazolidinediones e.g. Rosiglitazline</td>
<td>C</td>
<td>None reported but</td>
<td>Unknown</td>
<td>Stop at conception</td>
</tr>
</tbody>
</table>
Insulin requirements in pregnancy will fluctuate and are unpredictable

63 women with type 1 diabetes

Garcia-Paterson et al. Diabetologia 2012
Frequent glucose monitoring is recommended for women with type 1 and type 2

<table>
<thead>
<tr>
<th>Time</th>
<th>NICE 2015 (mmol/l)</th>
<th>ADA 2015 (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>&lt;5.3</td>
<td>3.3-5.4</td>
</tr>
<tr>
<td>1 hour post meal</td>
<td>&lt;7.8</td>
<td>5.4-7.1</td>
</tr>
<tr>
<td>2 hours post meal</td>
<td>&lt;6.4</td>
<td>&lt;6.4</td>
</tr>
</tbody>
</table>

If on insulin or glibenclamide – advise to maintain plasma glucose >4mmol/l

• Increase risk of hypoglycemia and impaired awareness in first trimester
HbA1C is not accurate during pregnancy

- Increased red cell turnover
- Changes in glycaemic range

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Healthy Pregnancy Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>&lt;5.3%</td>
</tr>
<tr>
<td>Second</td>
<td>&lt;7.8%</td>
</tr>
<tr>
<td>Third</td>
<td>&lt;5.6%</td>
</tr>
</tbody>
</table>

- DO not use HbA1C in second or third trimester to assess control
- Target <6.0%
Ketonaemia testing is recommended more readily

<table>
<thead>
<tr>
<th></th>
<th>Time Interval</th>
<th>Incidence, % (No.)</th>
<th>Perinatal Mortality Rate, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lufkin et al. (1)</td>
<td>1950–1979</td>
<td>7.9 (18/228)</td>
<td>27.8 (5/18)</td>
</tr>
<tr>
<td>Kilvert et al. (2)</td>
<td>1971–1990</td>
<td>1.7 (11/635)</td>
<td>22</td>
</tr>
<tr>
<td>Montoro et al. (3)</td>
<td>1972–1987</td>
<td>3.9 (22/560)</td>
<td>35 (7/20)</td>
</tr>
<tr>
<td>Chauhan et al. (4)</td>
<td>1976–1981</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td>1986–1991</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cullen et al. (5)</td>
<td>1985–1995</td>
<td>2 (11/520)</td>
<td>9 (1/11)</td>
</tr>
</tbody>
</table>

Diabetic Ketoacidosis is associated with increased perinatal mortality

Women with type 1 diabetes should be advised to test for ketonaemia if they become hyperglycaemic or unwell
Antenatal care – running the marathon!

Control blood sugar

Multi-disciplinary Care:
Midwives
Obstetricians
Diabetologist
Nephrologist
Nurses
Dieticians
Ophthalmologists
...

Monitor kidney & retinal function
OVER TO DR BRAMHAM!!!!
Diabetic retinopathy – Progression in pregnancy

**Assess at**
- a) First visit (if not done within last 3 months)
- b) At 28 weeks
- c) If present at first antenatal visit additional assessment at 16-20 weeks

- Retinopathy is not a contraindication to a vaginal delivery
- Lazer treatment is safe in pregnancy

**Risk factors for retinopathy progression**
- Established disease
- Anaemia
- Diastolic hypertension

---

**Table 3 – Comparison of incidences of short-term progression of any retinopathy between pregnant and nonpregnant women**

<table>
<thead>
<tr>
<th>Group</th>
<th>Not pregnant</th>
<th>Pregnant</th>
<th>OR†</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>With worse retinopathy</td>
<td>Total</td>
<td>With worse retinopathy</td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td>2,950</td>
<td>693 (23)</td>
<td>124</td>
<td>39 (31)</td>
<td>1.62</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Conventional</td>
<td>5,605</td>
<td>1,742 (31)</td>
<td>73</td>
<td>37 (51)</td>
<td>2.54</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are n or n (%) unless otherwise indicated. *Progression is relative to the pregnancy-free ETDRS level 6 and 12 months prior; †OR obtained from a GEE logistic regression model; ‡model adjusted for the prepregnancy retinopathy status, the recent change in HbA1c from the prior visit, and time of visit during study.

DCCT Study Diabetes Care 2000
Management of Proteinuria

Case 1

23 year old Type 1 Diabetes (HbA1C 9.8%)
Protein: Creatinine Ratio 1240mg/mmol at 20 weeks’

Thromboprophylaxis: recommended by NICE for proteinuria >5g/24 hours
Should be considered in context of other risk factors
Frusemide 20mg od
Proteinuria

Progression of Proteinuria

- N=11 Cr range 1.8-2.5mg/dl (159-221µmol/l)
  - Early pregnancy 18% nephrotic range (Median 2.4g/24hrs (0.2-8.0)
  - Late pregnancy 72% nephrotic range (Median 5.6g/24hrs (0.2-14.4)
- Worsening proteinuria in 82%

Purdy et al Diabetes Care 1996

Diabetic pre-eclampsia n= 26
Non diabetic pre-eclampsia n= 3
Diabetic normotensive n= 95
Non diabetic normotensive n= 21

Yu et al Diabetologica 2009
Antenatal care – running the marathon!

**Multi-disciplinary Care:**
- Midwives
- Obstetricians
- Diabetologist
- Nephrologist
- Nurses
- Dieticians
- Ophthalmologists
- ...

- Control blood sugar
- Control blood pressure
- Monitor kidney & retinal function
Blood pressure targets

Tight blood pressure control (Diastolic <85 mmHg) better maternal outcomes and no adverse impact on babies

Magee NEJM 2015
Target blood pressure for women with diabetes

Target Blood Pressure - Controversial

ADA Guidelines
• Systolic 110-129mmHg
• Diastolic 65-79mmHg

Canadian Guidelines
• Systolic 130-139mmHg
• Diastolic 80-89mmHg
Pre-eclampsia Risk Spectrum

- History term PE
- History preterm PE
- Non diabetic CKD

Aspirin / Vit D / Ca Prophylaxis

- Multiparous women
- Type 1 Diabetes
- Obesity
- Mild chronic hypertension
- Nulliparous women
- Diabetic Nephropathy
Rate of pre-eclampsia according to renal aetiology

Pregnancy Outcomes – Diabetic Nephropathy

Danish Prospective Cohort Study

Ekbom et al Diabetes Care 2001
Pregnancy outcomes: Normoalbuminuria v microalbuminuria

Danish population study 1993-1999

Independent predictors of pre-eclampsia

- Microalbuminuria OR 4.0 (95% CI 2.2-72)
- Nulliparity OR 3.1 (95% CI 1.9-5.3)
- Third trimester HbA1C increase by 1% OR 1.3 (95% CI 1.1-1.5)

Excluded
- Urine albumin >300mg/24 hrs
- Women taking antihypertensives

Jensen et al Diabetes Care 2012
Aspirin for Pre-eclampsia

Daily aspirin dose could lower pre-eclampsia risk in pregnant women

Low dose taken by women at risk of pre-eclampsia throughout pregnancy more than halves chances of premature birth, finds study

- Used screening test algorithm that combines 17 variables to stratify risk then randomised to 150 mg aspirin or placebo

Rolnik NEJM 2017
Pre-eclampsia – Novel biomarkers

Healthy Blood Vessel

Blood flow

- FLT-1
- PIGF
- VEGF
- sFLT-1
- ENDOGLIN (ENG)
- Transforming Growth Factor (TGF-β I)
- Transforming Growth Factor (TGF-β II)
- Soluble Endoglin (sEng)

Increased blood pressure
PROGNOSIS – Prospective International Cohort Study

Zeisler NEJM 2016
## Table 2. Validation of a Cutoff Point of 38 for the sFlt-1:PlGF Ratio in Predicting Preeclampsia.

<table>
<thead>
<tr>
<th>Preeclampsia</th>
<th>Development Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 1 wk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value: rule out</td>
<td>98.9 (97.3–99.7)</td>
<td>99.3 (97.9–99.9)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88.2 (72.5–96.7)</td>
<td>80.0 (51.9–95.7)</td>
</tr>
<tr>
<td>Specificity</td>
<td>80.0 (76.1–83.6)</td>
<td>78.3 (74.6–81.7)</td>
</tr>
<tr>
<td><strong>Within 4 wk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value: rule in</td>
<td>40.7 (31.9–49.9)</td>
<td>36.7 (28.4–45.7)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74.6 (62.5–84.5)</td>
<td>66.2 (54.0–77.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>83.1 (79.3–86.5)</td>
<td>83.1 (79.4–86.3)</td>
</tr>
</tbody>
</table>
## Hypertension in Pregnancy NICE Guidelines

**with additional diagnostic test for the PARROT trial**

<table>
<thead>
<tr>
<th>Mild hypertension</th>
<th>Moderate hypertension</th>
<th>Severe hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP up to 149/99 mmHg</td>
<td>BP 150/100–159/109 mmHg</td>
<td>BP ≥ 160/110 mmHg</td>
</tr>
<tr>
<td>• Do not admit to hospital.</td>
<td>• Do not admit to hospital.</td>
<td>• Admit to hospital until BP ≤ 159/109 mmHg and treat hypertension to keep BP &lt; 150/80–100 mmHg.</td>
</tr>
<tr>
<td>• BP up to 149/99 mmHg</td>
<td>• Treat hypertension to keep BP &lt; 150/80–100 mmHg.</td>
<td>• Measure BP at least x4/ day</td>
</tr>
<tr>
<td>• Do not treat hypertension.</td>
<td>• Measure BP at least x2/ wk.</td>
<td>• Test for proteinuria daily</td>
</tr>
<tr>
<td>• Measure BP no more than x1/wk</td>
<td>• Test for proteinuria at each visit</td>
<td>• Test kidney function, electrolytes, FBC, transaminases, bilirubin.</td>
</tr>
<tr>
<td>• Test for proteinuria at each visit</td>
<td>• Test kidney function, electrolytes, FBC, transaminases, bilirubin.</td>
<td>• No further blood tests if no subsequent proteinuria.</td>
</tr>
<tr>
<td>• Carry out routine antenatal blood tests.</td>
<td>• No further blood tests if no subsequent proteinuria.</td>
<td>• Arrange fetal USS</td>
</tr>
<tr>
<td>• If presenting before 32/40, or at high risk of pre-eclampsia, test for proteinuria and measure BP x2/ wk.</td>
<td>• Arrange fetal USS</td>
<td></td>
</tr>
</tbody>
</table>

**Continue care as in guidelines pathway; integrate additional information from PI GF test as shown below**

<table>
<thead>
<tr>
<th>PI GF &gt;100</th>
<th>PI GF 12-100</th>
<th>PI GF &lt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL</strong></td>
<td><strong>LOW</strong></td>
<td><strong>VERY LOW</strong></td>
</tr>
<tr>
<td>CONTINUE WITH USUAL MANAGEMENT</td>
<td>CONSIDER INCREASED SURVEILLANCE</td>
<td>ASSESS AS PRE-ECLAMPSIA</td>
</tr>
</tbody>
</table>

*Algorithm version 3.0 Jan 2016*
Placental Growth Factor in Clinical Practice

Stepped-wedge cluster randomised controlled trial
11 UK maternity units (3000-9000 deliveries per annum)
Women presenting to maternity services with suspected pre-eclampsia

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Revealed Group</th>
<th>Concealed Group</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women diagnosed with pre-eclampsia n (%)</td>
<td>N= 205 (36.8%)</td>
<td>N= 155 (34.8%)</td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis of pre-eclampsia (for those diagnosed) (days) Median (IQR)</td>
<td>1.9 (0.5, 9.2)</td>
<td>4.1 (0.8, 14.7)</td>
<td>0.39* (0.17-0.91)</td>
</tr>
</tbody>
</table>

*adjusted ratio of means

<table>
<thead>
<tr>
<th>Maternal Adverse Outcome</th>
<th>Revealed Group N= 573</th>
<th>Concealed Group N= 446</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal adverse outcomes n of women (%) *</td>
<td>22 (3.8%)</td>
<td>24 (5.4%)</td>
<td>aOR 0.32 (0.11-0.96)</td>
</tr>
</tbody>
</table>

*As defined by the fullPIERS consensus
Diagnosis of Pre-eclampsia – Anti angiogenic factors

Elevated sFlt-1, Low PLGF and elevated sFLt-1:PIGF precede pre-eclampsia in women with type 1 diabetes

BUT endoglin is elevated in women with type 1 diabetes regardless of onset of pre-eclampsia

? Contributes to increase risk

Yu et al Diabetologica 2009
Antenatal care – running the marathon!

Multi-disciplinary Care:
- Midwives
- Obstetricians
- Diabetologist
- Nephrologist
- Nurses
- Dieticians
- Ophthalmologists
- ...
Placental / Fetal imaging

**Umbilical Artery**
- PI: 2.93
- RI: reverse flow
- TAMX [cm/s]:
- SD ratio:
- EDF: reverse flow

**L. Middle Cerebral A.**
- PI: 1.13
- RI:
- TAMX [cm/s]:
- SD ratio:
- Vmax [cm/s]: 62.6

Reliable in CKD, Piccoli et al NDT 2013, Bramham et al Kidney Int 2016
Finishing the marathon
Diabetic Nephropathy Pregnancy Outcomes - Summary

Pre-eclampsia + Caesarean Section = Fetal loss

Preterm delivery + Low Birth Weight
Intrapartum care

- Diabetes is not a contraindication to antenatal steroids for fetal lung maturity – will need increased insulin and close monitoring

- Not for betamimetic tocolytics

- Anaesthetic assessment in third trimester if obese or autonomic neuropathy

- Aim for plasma glucose 4-7mmol/l during labour

- Intravenous insulin and dextrose recommended after onset of established labour

- **Offer delivery between 37⁺⁰ – 38⁺⁶ weeks’ if no complications**
- **Consider delivery before 37 weeks if maternal or fetal complications**
Neonatal Outcomes
Neonatal care

Hospital delivery recommended

Blood glucose monitoring 2-4 hours

Complications
• Polycythaemia
• Hyperbilirubinaemia
• Hypocalcaemia
• Hypomagnesiaemia

Vigilance for undiagnosed congenital heart disease

Breastfeeding Compatible Medication
• Metformin
• Glibenclamide
• Insulins

ENALAPRIL  Redman Eur J Clin Pharm 1990

BUT Reduced insulin requirements postpartum
Neonatal Outcomes
Neonatal outcomes in women with pre-existing diabetes

1548 pregnancies with pre-existing diabetes compared 393,844 without 1996-2008

### Table 1  RR of a fetal or infant death (in normally formed singleton offspring) associated with maternal pre-existing diabetes in the North of England during 1996–2008

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Without pre-existing diabetes</th>
<th>With pre-existing diabetes</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Prevalence (95% CI) per 1,000 deliveries/live births</td>
<td>Cases</td>
<td>Prevalence (95% CI) per 1,000 deliveries/live births</td>
</tr>
<tr>
<td>Fetal or infant death</td>
<td>3,988</td>
<td>10.1 (9.8, 10.4)</td>
<td>56</td>
<td>36.2 (27.4, 46.7)</td>
</tr>
<tr>
<td>Fetal death</td>
<td>2,582</td>
<td>6.5 (6.3, 6.8)</td>
<td>46</td>
<td>29.7 (21.8, 39.4)</td>
</tr>
<tr>
<td>Late miscarriage</td>
<td>796</td>
<td>2.0 (1.9, 2.2)</td>
<td>5</td>
<td>3.2 (1.0, 7.5)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1,786</td>
<td>4.5 (4.3, 4.7)</td>
<td>41</td>
<td>26.5 (19.1, 35.8)</td>
</tr>
<tr>
<td>Antepartum stillbirth</td>
<td>1,593</td>
<td>4.0 (3.8, 4.2)</td>
<td>38</td>
<td>24.5 (17.4, 33.5)</td>
</tr>
<tr>
<td>Intrapartum stillbirth</td>
<td>193</td>
<td>0.5 (0.4, 0.6)</td>
<td>3</td>
<td>1.9 (0.4, 5.7)</td>
</tr>
<tr>
<td>Infant death</td>
<td>1,406</td>
<td>3.6 (3.4, 3.8)</td>
<td>10</td>
<td>6.7 (3.2, 12.2)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>904</td>
<td>2.3 (2.1, 2.5)</td>
<td>6</td>
<td>4.0 (1.5, 8.7)</td>
</tr>
<tr>
<td>Postneonatal death</td>
<td>502</td>
<td>1.3 (1.2, 1.4)</td>
<td>4</td>
<td>2.7 (0.7, 6.8)</td>
</tr>
</tbody>
</table>

Tennant et al Diabetologica 2014
Improvement in outcomes from 2002 to 2015

**Fig. 3** Stillbirth rate during the NPID audit 2015 compared with CEMACH 2002/2003 for women with type 1 and type 2 diabetes. Data presented are stillbirth rates per 1000 births with 95% CI. Dashed line, stillbirth rate for the general maternity population for 2015 (based on data from the Office for National Statistics [12]).
Fig. 2 Relationships for achievement of glycaemic control targets (HbA₁₀ < 6.5% [48 mmol/mol]) with (a) preterm delivery before 37 weeks’ gestation and (b) rates of LGA in infants (customised birthweight >90th percentile). Black bars, type 1 diabetes; grey bars, type 2 diabetes.
### Pregnancy outcomes – Type 1 v Type 2 diabetes

<table>
<thead>
<tr>
<th>Complications in pregnancy</th>
<th>Type 2 diabetes</th>
<th>Type 1 diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>6 (10)</td>
<td>12 (5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4 (7)</td>
<td>30 (13)</td>
<td>0.26</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>22 (36)</td>
<td>123 (51)</td>
<td>0.04</td>
</tr>
<tr>
<td>Perinatal outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>4 (6.6)</td>
<td>7 (2.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>4 (6.7)</td>
<td>4 (1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>38.0 (37–39)</td>
<td>37.3 (36–38)</td>
<td>0.03</td>
</tr>
<tr>
<td>Birth &lt;34 weeks’ gestation*</td>
<td>8 (14)</td>
<td>17 (7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Birth &lt;37 weeks’ gestation*</td>
<td>18 (31)</td>
<td>87 (38)</td>
<td>0.29</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>3,600 (3,095–3,990)</td>
<td>3,595 (3,064–3,925)</td>
<td>0.79</td>
</tr>
<tr>
<td>Large for gestational age*</td>
<td>33 (56)</td>
<td>117 (51)</td>
<td>0.54</td>
</tr>
<tr>
<td>Small for gestational age*</td>
<td>1 (2)</td>
<td>9 (4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Birth weight &gt;4,500 g*</td>
<td>5 (8)</td>
<td>11 (5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Neonatal jaundice*</td>
<td>13 (22)</td>
<td>40 (18)</td>
<td>0.35</td>
</tr>
<tr>
<td>Respiratory difficulties*</td>
<td>12 (20)</td>
<td>52 (23)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*The total of live-born singleton infants was 59 for type 2 diabetes and 228 for type 1 diabetes.

Clausen et al Diabetes Care 2005

Comparable pregnancy outcomes between women with nephropathy Type 1 v 2

Damm et al Diabetes Care 2014
Neonatal Outcomes – Diabetic Nephropathy


Piccoli et al Diabetes Studies Rev 2013

Factors influencing pregnancy outcomes in women with diabetic nephropathy

Independent predictors of preterm delivery <37 weeks’

• First trimester blood pressure <130/80mmHg
• First trimester proteinuria >1g/24hrs or 2 or 3+ protein on urinalysis
• Last HbA1c before delivery

Klemmeti et al Diabetologica 2015
But – small cohort studies – possibly?

Table 2. Comparison of pregnancy outcomes in studies of pregnant type 1 diabetic women with microalbuminuria covering the same geographical area in Eastern Denmark

<table>
<thead>
<tr>
<th>Antihypertensive Therapy Strategy</th>
<th>Ekbom et al., 2001 (25)</th>
<th>Nielsen et al., 2006 (54)</th>
<th>Nielsen et al., 2009 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Eclampsia</td>
<td>BP &gt;140/90 mmHg</td>
<td>BP &gt;135/85 mmHg</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP &gt;95 mmHg</td>
<td>UAE &gt;2 g/24 h</td>
<td>UAE ≥300/24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACE Inhibitor before Pregnancy</td>
<td>ACE Inhibitor before Pregnancy</td>
</tr>
<tr>
<td>Number</td>
<td>26</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>19±5</td>
<td>18±8</td>
<td>15±10</td>
</tr>
<tr>
<td>HbA1c at inclusion (%)</td>
<td>8.1±0.9</td>
<td>6.8±0.5</td>
<td>7.3±1.5</td>
</tr>
<tr>
<td>Week of onset of antihypertensive therapy</td>
<td>29 (20–34)</td>
<td>13 (Before-34)</td>
<td>Before (Before-14)</td>
</tr>
<tr>
<td>Patients on antihypertensive therapy during pregnancy</td>
<td>9 (35)</td>
<td>10 (50)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>ACE inhibitor before pregnancy</td>
<td>5 (19)</td>
<td>9 (45)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Systolic BP at inclusion (mmHg)</td>
<td>121±13</td>
<td>121±14</td>
<td>117±14</td>
</tr>
<tr>
<td>Diastolic BP at inclusion (mmHg)</td>
<td>71±8</td>
<td>73±8</td>
<td>74±8</td>
</tr>
<tr>
<td>UAE (mg/24 h)</td>
<td>69 (16–278)</td>
<td>74 (30–287)</td>
<td>91 (30–198)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>11 (42)</td>
<td>4 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Preterm delivery before 34 wk</td>
<td>6 (23)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Preterm delivery before 37 wk</td>
<td>16 (62)</td>
<td>8 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3124±767</td>
<td>3279±663</td>
<td>3471±670</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major congenital malformations</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Long term maternal outcomes
Pre-existing nephropathy Progression

No difference in rate of decline between women with and without pregnancies over 16 years

Rossing et al Diabetologica 2002
Renal Disease Progression: Postpartum – 3 months

Adaptation to pregnancy N=6 (5 women)
- Pre-pregnancy Cr Cl 80mls/min/1.73m² (Range 70-91)
- Postpartum Cr Cl 78mls/min/1.73m² (Range 70-92)

No adaptation to pregnancy N=8 (7 women)
- Pre-pregnancy Cr Cl 61mls/min/1.73m²
- (Range 37-73)
- Postpartum Cr Cl 39mls/min/1.73m² (Range 22-68) ~ 36% decline

Risk factors for progression
- BP during pregnancy tended to be higher in non adapters
- BP significantly higher in week before delivery

? Role for tight hypertensive control / ? Contribution from placental disease

7/11 (64%) progressed to End Stage in 6-57 months after delivery

Biesenback et al J of Nephrology 1999
Comparison of progression with other CKD

82 pregnancies in 62 women
Mean Cr $1.9\pm0.8$mg/dl (168$\pm$71μmol/l)

11 pregnancies in 11 women
Cr range 1.8-2.5mg/dl (159-221μmol/l)

Jones and Hayslett NEJM 2006
Purdy et al Diabetes Care 1996
35% of the cohort had died during the 16 year follow-up period

**Cardiovascular morbidity**
- 8/14 women with diabetic nephropathy had significant atherosclerotic disease (Bagg et al 2003)
Summary

- Multidisciplinary team work is essential
- Pre-pregnancy counselling
  - Aggressive treatment before conception
  - Avoidance of unplanned pregnancy
- Hypertensive control during pregnancy
- Glycaemic control during pregnancy
- Risk of disease progression at higher GFR than CKD
Thank you
How to optimise outcomes: Hypertension

Suboptimal blood pressure associated with preterm delivery and nephrotic range proteinuria

MAP <110mmHg

But above target group had:
- Higher Creatinine 1.23 +/- 0.17 v 0.85 +/- 0.06 mg/dL
- Higher proteinuria 4.69 +/- 1.08 v 1.65 +/- 0.43 g/24 h

Carr et al Am J Hyperten 2006
How to optimise outcomes: Hypertension

Intensive treatment in 41 women microalbuminuria or nephropathy

Type 1: N=15, Type 2: N=26

• Blood pressure target <135/85mmHg
• Proteinuria target <300mg/24hrs

More women with type 1 diabetes required antihypertensives

Achieved median BP in early and late pregnancy 128/70mmHg

Only 1/41 women developed nephrotic proteinuria / Stable serum creatinine

But – no differences in preterm delivery and birth weight compared with historic data

Damm et al Diabetes Care 2014
How to optimise outcomes: Hypertension


More antihypertensive use pre-pregnancy and during pregnancy – but frequently discontinued in early pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>1988–1999 (n=65)</th>
<th>2000–2011 (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS inhibitor used before pregnancy</td>
<td>16 (26.2) [61]</td>
<td>24 (55.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>34 (52.3)</td>
<td>18 (41.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepregnancy</td>
<td>1.50 (0.45–7.70) [13]</td>
<td>0.80 (0.34–4.03) [13]</td>
<td>0.42</td>
</tr>
<tr>
<td>1st trimester</td>
<td>1.55 (0.40–11.50) [28]</td>
<td>1.77 (0.33–10.40) [17]</td>
<td>0.59</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>2.53 (0.58–22.20) [40]</td>
<td>2.44 (0.42–18.50) [29]</td>
<td>0.63</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>5.90 (0.37–22.70) [58]</td>
<td>4.22 (0.45–19.80) [40]</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Klemetti et al Diabetologica 2015
**Antenatal care**

**Control blood sugar**
- Tight targets
- Avoiding hypo’s
- Unpredictably increasing requirements (5% per week)
- Caution with HbA1c

**Control blood pressure**
- SBP 110-130mmHg
- DBP 70-80mmHg
- Think PRE-ECLAMPSIA

**Monitor kidney and retinal function**
- Repeat retinopathy assessment at 28 weeks
- Monitor proteinuria
- Monitor serum creatinine (NOT eGFR)

**Multi-disciplinary Care:**
- Midwives
- Obstetricians
- Diabetologist
- Nephrologist
- Nurses
- Dieticians
- Ophthalmologists

**Monitor fetus**
- Usual monitoring regime
- PLUS…fetal cardiac scan
- Uterine artery dopplers
- Additional fetal growth scans