Pre-eclampsia – an evolution of understanding

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Senior Lecturer, Consultant Obstetrician
A Pregnant
Morbidity/Mortality

- Severe maternal morbidity/mortality preventable
  - Stroke
  - Severe hypertension
  - Eclampsia
  - Pulmonary oedema
  - Renal/Hepatic

- Enormous perinatal mortality/morbidity
  - FGR
  - Preterm delivery

- Early recognition/diagnosis
- Management pathways
Early recognition

### The North West Regional Guidelines for the Management of Severe Pre-eclampsia

#### Features of Severe Pre-eclampsia
- BP > 160/110 mmHg with at least 1+ proteinuria
- OR
- BP > 140/90 mmHg with significant proteinuria and symptoms including:
  - Headache
  - Visual disturbance
  - RUQ pain/vomiting
  - Clonus (>23 beats)
  - HELLP syndrome
  - Platelet < 100
  - ALT/AST > 70 u/L

#### Management of Severe Pre-eclampsia
- Measure BP every 15 minutes until stable consider continual monitoring with arterial line
- Continue antenatal hypertensive treatment
- Treat hypertension with IV labetolol, nitidipine (oral), IV hydralazine
- Monitor response to treatment (maternal & fetal wellbeing)
- Aim BP < 150/80-100 mmHg
- If BP controlled, do not routinely limit second stage

#### Anticonvulsants
- Give IV Magnesium Sulphate if woman with severe hypertension/pre-eclampsia has or previously had eclamptic fit
- Consider giving IV Magnesium Sulphate to women with severe pre-eclampsia, if birth planned within 24 hours
- Alternative anticonvulsants are not indicated in women with eclampsia

#### General Measures:
- Inform Consultant Obstetrician and Anaesthetist
- IV access
- Hourly MEWS
- Urinary catheter with urometer
- CTG monitoring as appropriate

#### Regimen for Magnesium Sulphate
- Loading dose 4g IV over 5-10 minutes, followed by infusion 1g/hour for 24 hours
- Further dose of 2-4g given over 5 minutes if recurrent seizures

#### Corticosteroids
- For fetal lung maturation:
  - If birth likely within 7 days in women with pre-eclampsia
  - Give 2 doses betamethasone 12mg IM 24 hrs apart between 24 and 34 weeks
  - Consider giving 2 doses betamethasone at 35-36 weeks

#### Fluid balance:
- Do not preload with IV fluids before establishing low-dose epidural analgesia and combined spinal epidural analgesia
- Limit maintenance fluids to 80mls/hr unless there is significant hemorrhage
- Do not use volume expansion

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This protocol was devised in November 2002 and was revised in February 2006, Nov 2008 & Feb 2011.
**PATHOPHYSIOLOGY**

- Decreased conversion of utero-placental arteries
- Abnormal placental development/function
- PLACENTAL DAMAGE
  - Release of Circulating Factors / Material
  - Altered Vascular Reactivity
  - Decreased endothelial dependent relaxation
  - Increased markers of endothelial dysfunction
- PRE-ECLAMPSIA
  - Maternal Immune System
  - Hypertension
  - Proteinuria
  - Inappropriate activation of clotting cascade
  - Liver/renal dysfunction
- IUGR

**PRE-ECLAMPSIA**

- Hypertension
- Proteinuria
- Inappropriate activation of clotting cascade
- Liver/renal dysfunction

**PLACENTAL DAMAGE**

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**IUGR**

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**Hypertension**

**Proteinuria**

**Liver/renal dysfunction**

**Inappropriate activation of clotting cascade**

**Decreased endothelial dependent relaxation**

**Increased markers of endothelial dysfunction**
Definitions

- New hypertension with:
  - Qualitative diagnosis of proteinuria
  - Evidence of biochemical or haematological abnormalities
    - Plts < 100 x10^8/l
    - Cr > 100 μmol/l
    - ALT > 80 μmol/l
  - Symptoms suggestive of end organ disease
  - (Fetal growth restriction)
- With and without severe features
General principles

• Absolute risk of adverse outcomes is low

• Supportive treatment:
  • Maintain safe blood pressure
  • Prevent/treat seizures
  • Avoid pulmonary oedema
  • Early identification multi-system disease – ALT, creatinine, platelets

• Deliver:
  • <34 weeks – expectant management WITH CARE PLAN
  • 34-37 weeks – uncertainty in the absence of severe features: PHOENIX
  • >37 weeks – delivery should be offered (Hypitat)
Prediction of adverse outcome

FullPIERS model predictors of adverse maternal outcomes:
• gestational age
• chest pain or dyspnoea
• oxygen saturation
• platelet count
• creatinine
• aspartate transaminase

Von Dadelszen et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. The Lancet, Volume 377, Issue 9761, Pages 219 - 227
Pre-eclampsia Integrated Estimate of Risk (PIERS)

Gestational age (at delivery, if de novo postpartum pre-eclampsia):

32 weeks 1 days

Did the patient have chest pain or dyspnoea? No

SpO2* (use 97% if unknown): 99 %

Platelets (×10^9/L): 118

Creatinine (μmol/L): 132

AST (U/L): 22

* - Oxygen saturation by pulse oximetry

Probability of adverse maternal outcomes: 

https://piers.cfri.ca/PIERSCalculatorH.aspx
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Probability of adverse maternal outcomes: 2.5 %

https://piers.cfri.ca/PIERSCalculatorH.aspx
## Adverse Outcomes (n=346)

<table>
<thead>
<tr>
<th></th>
<th>&lt;35</th>
<th>35-37</th>
<th>&gt;37</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final adjudicated diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number of women</strong></td>
<td>176</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td><strong>Number with any maternal complication</strong></td>
<td>91 (52%)</td>
<td>33 (41%)</td>
<td>28 (31%)</td>
</tr>
<tr>
<td>Systolic blood pressure ≥160mmHg</td>
<td>76</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke; hypertensive encephalopathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intubation (other than for caesarean section)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelets &lt;50×10⁹/L (without transfusion)</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Liver Dysfunction (Alanine transaminase ≥70IU/L)</td>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine &gt;150 μmol/L</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Obstetric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Major postpartum haemorrhage</td>
<td>7</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

No DIC, hepatic rupture, dialysis, retinal detachment

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Eclampsia

- Difficult to predict
- No correlation with other signs
- Headache, visual disturbance
- Clonus ≥3 beats
Stroke

- Strongest correlation with **SYSTOLIC** blood pressure

- No comparison group
- Only 2 with chronic hypertension
- 54% died
- 64% HELLP

Martin et al AMJOG 2005
**Pre-stroke hypertension**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pregnancy Baseline</th>
<th>Prestroke</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic BP</td>
<td>110.9 ± 10.7 (n = 25)</td>
<td>175.4 ± 9.7 (n=24)</td>
<td>64.4 ± 11.6 (n = 22)</td>
</tr>
<tr>
<td>Systolic BP range</td>
<td>90–136</td>
<td>159–198</td>
<td>39–85</td>
</tr>
<tr>
<td>Systolic BP % ≥ 160</td>
<td>0</td>
<td>95.8</td>
<td></td>
</tr>
<tr>
<td>Mean diastolic BP</td>
<td>67.4 ± 6.5 (n = 25)</td>
<td>98.0 ± 9.0 (n = 24)</td>
<td>30.6 ± 9.6 (n = 22)</td>
</tr>
<tr>
<td>Diastolic BP range</td>
<td>58–80</td>
<td>81–113</td>
<td>8–53</td>
</tr>
<tr>
<td>Diastolic BP % ≥ 110</td>
<td>0</td>
<td>12.5 (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP % ≥ 105</td>
<td>0</td>
<td>20.8 (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Mean MAP</td>
<td>81.7 ± 7.7 (n=25)</td>
<td>123.9 ± 6.6 (n=24)</td>
<td>42.1 ± 8.2 (n = 21)</td>
</tr>
<tr>
<td>MAP range</td>
<td>69–98</td>
<td>114–138</td>
<td>25–57</td>
</tr>
<tr>
<td>MAP % ≥ 125</td>
<td>0</td>
<td>45.8</td>
<td></td>
</tr>
<tr>
<td>MAP % ≥ 130</td>
<td>0</td>
<td>20.8</td>
<td></td>
</tr>
</tbody>
</table>

Recommend treat sBP >150 mmHg

Martin et al AMJOG 2005
Severe hypertension

- Oral labetalol 200 mg max 2 doses – effect within 1 hour
- Bolus IV labetalol (50mg 10 min intervals x 4) – effect within 45 minutes
- IV hydralazine (2.5mg 20 min intervals max 20mgs)
- Oral nifedipine 10 mg 4 hourly
- Maintain BP with hydralazine infusion
- Maintain BP with labetalol infusion
- Consider modified release/long acting nifedipine

- Consider cardiac output changes – peri partum/GH/PET
- CAUTION magnesium sulphate
Few RCTS

- 15 randomised controlled trials (915 women)
- Most trials in pregnancy compared oral/sublingual nifedipine capsules (8-10 mg) with parenteral hydralazine or labetalol.
- Oral nifedipine:
  - treatment success in most women, similar to hydralazine (84%) and labetalol (100%)
  - Less than 2% of women treated with nifedipine experienced hypotension.
  - There were no differences in adverse maternal or fetal outcomes.
- Target BP was achieved ~ 50% of the time with oral labetalol or methyldopa

Firoz et al BJOG 2014
Pulmonary Oedema

- **Antenatal**
  - Record UO – don’t intervene
  - Fluid restriction if severe disease
- **Postnatal**
  - Fluid shifts take 24-48 hours post delivery
  - Intravascular volume depletion
  - Replace blood loss
  - Oliguria is normal
  - NO FLUID CHALLENGES (1st 24 hours)
Fluid balance

Fluid → Healthy blood vessel → Urine oliguria

Normal pulmonary function

Vasodilation → normal BP ↑BP

Vasodilation

Vasoconstriction
## Fluid Management

<table>
<thead>
<tr>
<th>Year</th>
<th>Cerebral</th>
<th>Pulmonary</th>
<th>Hepatic</th>
<th>Renal</th>
<th>Other</th>
<th>Total</th>
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<tbody>
<tr>
<td>70-72</td>
<td>25</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>47</td>
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<tr>
<td>73-75</td>
<td>23</td>
<td>7</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>49</td>
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<tr>
<td>76-78</td>
<td>21</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>33</td>
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<tr>
<td>79-81</td>
<td>17</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>36</td>
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<tr>
<td>82-84</td>
<td>21</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>25</td>
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<tr>
<td>85-87</td>
<td>11</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>26</td>
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<tr>
<td>88-90</td>
<td>14</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>27</td>
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<tr>
<td>91-93</td>
<td>5</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>94-97</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>20</td>
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<tr>
<td>97-99</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>16</td>
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<tr>
<td>00-02</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>14</td>
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<td>03-05</td>
<td>12</td>
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<td>2</td>
<td>0</td>
<td>4</td>
<td>18</td>
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<tr>
<td>06-08</td>
<td>12</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>19</td>
</tr>
</tbody>
</table>
Persistent oliguria

- Check for evidence of bleeding
- Exclude
- Check renal function 6-12 hourly
- If UO ≤ 100mls over 4 hours continue fluid restriction
- If creatinine increasing or UO < 100mls over 4 hours consider frusemide and input/output matching

Mehrabadi et al. Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study. BMJ 2014;349:g4731 doi: 10.1136/bmj.g4731
IUGR

Decreased conversion of utero-placental arteries
Abnormal placental development/function
PLACENTAL DAMAGE
Release of Circulating Factors / Material
Deterioration vascular function
Multisystem Disorder

Maternal Immune System
Hypertension
Proteinuria
Inappropriate activation of clotting cascade
Liver/renal dysfunction

Alteration angiogenic factors
sFlt
PIGF

Increased markers of endothelial dysfunction
Decreased endothelial dependent relaxation
Deterioration vascular function
Liver/renal dysfunction
Inappropriate activation of clotting cascade
Proteinuria
Hypertension
Maternal Immune System

MULTISYSTEM DISORDER

IUGR

Release of Circulating Factors / Material
Diagnostic accuracy of PIGF in suspected pre-eclampsia

- Placental growth factor (PIGF) is an effective diagnostic test for preeclampsia (PELICAN study)
- 96% sensitivity PE delivered in 14 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No adverse outcome</th>
<th>Adverse outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>sFlt1/PIGF ratio</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (Q1, Q3)</td>
<td></td>
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<tr>
<td>Any outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57</td>
<td>47.5 (9.7, 87.0)</td>
<td>42</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELLLP</td>
<td>94</td>
<td>70.1 (22.1, 225.3)</td>
<td>5</td>
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<tr>
<td>Transaminitis</td>
<td>82</td>
<td>65.2 (20.7, 145.8)</td>
<td>17</td>
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<tr>
<td>Thrombocytopenia</td>
<td>92</td>
<td>70.1 (22.3, 220.1)</td>
<td>7</td>
</tr>
<tr>
<td>DIC</td>
<td>99</td>
<td>73.8 (22.4, 228.8)</td>
<td>0</td>
</tr>
<tr>
<td>Abruptio</td>
<td>94</td>
<td>73.2 (22.4, 225.3)</td>
<td>5</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>98</td>
<td>77.9 (22.4, 228.8)</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>99</td>
<td>73.8 (22.4, 228.8)</td>
<td>0</td>
</tr>
<tr>
<td>ARF</td>
<td>94</td>
<td>73.2 (22.1, 225.3)</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>96</td>
<td>73.2 (22.3, 235.0)</td>
<td>3</td>
</tr>
<tr>
<td>Maternal death</td>
<td>99</td>
<td>73.8 (22.4, 228.8)</td>
<td>0</td>
</tr>
<tr>
<td>Fetal/neonatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA ≤10%</td>
<td>79</td>
<td>72.3 (22.1, 202.1)</td>
<td>18</td>
</tr>
<tr>
<td>Abnormal umbilical Doppler</td>
<td>88</td>
<td>65.9 (22.0, 187.3)</td>
<td>11</td>
</tr>
<tr>
<td>Neonatal death (&lt;28 days)</td>
<td>96</td>
<td>77.9 (23.5, 227.1)</td>
<td>1</td>
</tr>
</tbody>
</table>

Sequential sFlt/PlGF ratio in women with pre-eclampsia

Clinical evaluation

- Evaluated PlGF in 264 high-risk women
  - 62 had a very low PlGF (<12 pg/ml)
  - 77 had a borderline PlGF (12-100 pg/ml)
  - 125 women had a normal PlGF (>100 pg/ml)

Outcomes:
- <12: 38/61 delivered <34 weeks; 35/55 <3rd centile
- 12-100: 7/77 delivered <34 weeks; 22/72 <3rd centile
- <12: Median time to delivery 13 days (0-54); 48% very low >14 days

PIGF-based testing to help diagnose suspected pre-eclampsia (Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PIGF plus Kryptor PE ratio)

Diagnostics guidance
Published: TBC
nice.org.uk/guidance/dg23
# Examples

<table>
<thead>
<tr>
<th></th>
<th>LD</th>
<th>XO</th>
<th>VJ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Underlying diagnosis</strong></td>
<td>Diabetic nephropathy</td>
<td>Renal hypertension, BMI 42</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td><strong>Early pregnancy (&lt;20 weeks)</strong></td>
<td>Hypertension, proteinuria Cr 65, PCR 35-50mg/mmol</td>
<td>Hypertension, proteinuria Cr 120, PCR 50-100mg/mmol</td>
<td>Hypertension, proteinuria Cr 160, PCR 350-450mg/mmol</td>
</tr>
<tr>
<td><strong>Presenting complication</strong></td>
<td>Worsening hypertension, unstable diabetes, macrosomia, polyhydramnios</td>
<td>Worsening hypertension, bordeline ALT</td>
<td>Worsening hypertension, ‘normally’ grown infant</td>
</tr>
<tr>
<td><strong>PlGF</strong></td>
<td><strong>15 pg/mmol</strong></td>
<td><strong>354 pg/mmol</strong></td>
<td><strong>265 pg/mmol</strong></td>
</tr>
<tr>
<td><strong>Decision to deliver</strong></td>
<td>Delivery 35 weeks, falling insulin requirement</td>
<td>Deterioration renal function 34 weeks</td>
<td>‘Routine’ 37+ weeks</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Elective CS, low pH, oliguria</td>
<td>Induction, SVD</td>
<td>Induction, SVD</td>
</tr>
</tbody>
</table>
Conclusions

- Most maternal morbidity preventable
- Main cause of morbidity related to management of hypertension
- In real life pre-eclampsia is frequently complex and atypical
- Bad outcomes are difficult to predict
- New tests may help to reduce adverse outcomes in women with hypertensive disease in pregnancy
- PlGF identifies the placental involvement in pre-eclampsia not the maternal aspects of the disease
- Maternal (term) pre-eclampsia is still dangerous
- Perinatal loss is still a huge issue
Thank you