The medical management of pre-eclampsia
What we’ll consider

1. New thoughts on classification & diagnosis
2. Why is pre-eclampsia important?
3. When to deliver?
4. Management of hypertension & convulsion prophylaxis
5. The early post-partum period
6. Long-term issues
Mrs PE:

- 29 yr old previously well primigravida presents at 31 weeks gestation with asymptomatic BP 160 / 100 mmHg
  - BP 100/60 at 10 weeks gestation
  - Mother had hypertension in pregnancy,
    - now has essential hypertension
  - No symptoms, fetal movements plentiful
  - Urinalysis normal
  - Normal examination, reflexes
  - Fundal height 29cm

- Does she have pre-eclampsia?
How to diagnose pre-eclampsia
The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP

**Table 1**
The revised ISSHP classification (2013) for hypertensive disorders in pregnancy.

1. Chronic hypertension
2. Gestational hypertension
3. Pre-eclampsia – de novo or superimposed on chronic hypertension
4. White coat hypertension
The revised ISHAN definition of pre-eclampsia (2014) is:

Hypertension developing after 20 weeks gestation and the coexistence of one or more of the following new onset conditions:

1. Proteinuria
2. Other maternal organ dysfunction:
   - renal insufficiency (creatinine ≥90 umol/L)
   - liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain)
   - neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata)
   - haematological complications (thrombocytopenia, DIC, haemolysis)
3. Uteroplacental dysfunction
   - foetal growth restriction
Pre-eclampsia =
Hypertension (yes)
+ Proteinuria (yes/no)
+ Edema (No)
Can we use automated BP devices?

**Prospective Randomised study of Automated vs. Mercury BP in hypertensive pregnancy (PRAM study)**

A study of 220 women

**Similar maternal and fetal outcomes**

St George Hospital & University of NSW
Sydney. Australia

A liquid crystal display sphygmomanometer: 
A replacement for mercury sphygmomanometry at last?

<table>
<thead>
<tr>
<th></th>
<th>LC - Hg free</th>
<th>Automated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertensive (n=170)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ≤ 5mmHg</td>
<td>94%</td>
<td>75%</td>
<td>0.021</td>
</tr>
<tr>
<td>Diastolic ≤ 5mmHg</td>
<td>97%</td>
<td>61%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Normotensive (n=170)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ≤ 5mmHg</td>
<td>98%</td>
<td>70%</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic ≤ 5mmHg</td>
<td>99%</td>
<td>73%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

GK Davis, LM Roberts, G Mangos, MA Brown
St George Hospital and University of NSW, Sydney, Australia
Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension
Caroline S.E. Homer\textsuperscript{a}, Mark A. Brown\textsuperscript{b,c,d}, George Mangos\textsuperscript{b,c,d} and Gregory K. Davis\textsuperscript{b}

Table 3 Clinical outcomes more likely in non-proteinuric PE vs. proteinuric PE and gestational hypertension \( N=1348 \)

Non-proteinuric PE compared to proteinuric PE
More common in Non-proteinuric PE
\begin{itemize}
  \item Thrombocytopenia
  \item Liver Disease
\end{itemize}
Less common in Non-proteinuric PE
\begin{itemize}
  \item Severe hypertension
  \item Pre-term (<37 weeks) birth
  \item Perinatal mortality
\end{itemize}

Non-proteinuric pre-eclampsia endorsed by ACOG 2013
A blood test to diagnose pre-eclampsia?
Soluble FMS-like Tyrosine kinase 1 (sFlt1)

- Variant of VEGF receptor
- increased placental production in PE
  - mops up circulating VEGF and PlGF
  - leads to decreased circulating VEGF & PlGF
- VEGF depletion or antagonism known to lead to proteinuria
- sFLT1 given to pregnant rats caused proteinuria, hypertension, endotheliosisis, fibrin deposits

Maynard et al. JCI 2003;111:649-658
In preeclampsia, excess placental soluble Flt-1 binds circulating VEGF and PIGF. Prevents interaction with endothelial cell-surface receptors = endothelial cell dysfunction, decreased prostacyclin, nitric oxide release of procoagulant proteins - vWF, endothelin, cellular fibronectin, and thrombomodulin.

Predictive accuracy and correlation with duration of pregnancy of sFlt1/PIGF in pre-eclampsia.

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>sFlt1/PIGF&lt;85</th>
<th>sFlt1/PIGF&gt;85</th>
</tr>
</thead>
<tbody>
<tr>
<td>sFlt1/PIGF&lt;85</td>
<td>118</td>
<td>35</td>
</tr>
<tr>
<td>sFlt1/PIGF&gt;85</td>
<td>89</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>

Angiogenic Factors in Diagnosis, Management, and Research in Preeclampsia

- emerging role is risk stratification
  1. Elevated sFlt-1/PlGF in those destined for adverse outcomes within 2 weeks, especially preterm.
  2. The ratio alone outperformed BP, proteinuria, uric acid, ALT, platelet count, and creatinine.

- severest forms of preeclampsia associated with markedly elevated sFlt1/PlGF.

Gestation corrected Uric acid in pre-eclampsia and gestational hypertension

1610 hypertensive pregnant women.

significant associations (adjusted for parity):

1. Pre-term birth
2. SGA: especially in ‘benign’ gestational hypertension
3. Thrombocytopenia
4. Impaired GFR

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Serum uric acid (mmol/l)</th>
<th>Serum uric acid (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;32 weeks</td>
<td>&gt;0.24</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>32–35 weeks</td>
<td>&gt;0.27</td>
<td>&gt;4.5</td>
</tr>
<tr>
<td>36–37 weeks</td>
<td>&gt;0.29</td>
<td>&gt;4.9</td>
</tr>
<tr>
<td>≥38 weeks</td>
<td>&gt;0.33</td>
<td>&gt;5.6</td>
</tr>
</tbody>
</table>

Hawkins et al. BJOG Volume 119, Issue 4, pages 484–492, March 2012
St George hospital. Sydney.
Why is pre-eclampsia important?
Why the fuss?

- **Worldwide**
  - average of 134 maternal and 410 baby deaths daily (WHO).

- **USA 1998-2005**
  - hypertensive disorders 579 (12%) of 4693 maternal deaths

- **Netherlands**
  - 96% of cases maternal death had *substandard care* practices
    - BJOG 2008

- **UK**
  - The last triennial audit, 22 deaths from pre-eclampsia
    - 20 associated with *substandard care*; 14 considered avoidable
    - BJOG 2011;118(suppl 1):1-205
Mrs PE

- Ultrasound = 29 weeks growth; normal dopplers; AFI lower limit normal
- Creatinine 80umol/L; Uric acid 0.34mmol/L; ALT 30;
- Hb 130g/L; platelets 140,000
- Urine protein/creatinine ratio 18 mg/mmol
- BP 160/100 overnight
Should our patient be delivered now?
How to predict which women will have poor maternal or fetal outcomes
756 women GH or mild PE 36-41 weeks

difference 1 vs. 6 days to labour

Primary Outcome - Maternal – severe ht; PPH; eclampsia; HELLP

48% of expectant group ended up IOL – mostly severe ht

IOL group - Less primary outcome 29 vs. 42%; Less LSCS 14 vs. 19%

- Recommend IOL for GH or PE at 37 weeks
Should women with Early Onset Pre-eclampsia be delivered upon diagnosis?

- MEXPRE study – 8 Latin America countries; 267 severe PE, 28-33 weeks
  - 60% had BP > 160/110 at enrolment

- Steroids then delivery vs. expectant Rx to 34 weeks
  - Average prolongation 10 vs. 2 days

- Similar
  - PNM (9%)
  - Neonatal morbidity (55%) - RDS, IVH, NEC, neonatal sepsis.
  - Maternal morbidity (23%) - abruption, pulmonary edema, HELLP, renal insufficiency, eclampsia, DIC
    - No maternal deaths
Should women with Early Onset Pre-eclampsia be delivered upon diagnosis?

- Expectant group
  - More SGA (22vs 9%) and abruption

- Criticisms
  - Underpowered;
  - could have used more antihypertensives in expectant group
    - poorly controlled BP indication for delivery;
  - 42% were enrolled at 32-33 weeks anyway.
When we should deliver

1. An ‘expectant’ approach is reasonable in selected centres

2. Deliver when
   - Inability to control maternal BP
   - Evidence of maternal disease progression
   - Concerns about fetal wellbeing
Mrs PE

- Decision to prolong pregnancy

- Steroids given; oxprenolol for BP control

- 24 hrs later:
  - BP 180/116
  - Headache with hyper-reflexia & clonus
  - Platelets 110,000; ALT 280; Hb 140g/L
  - Creatinine 100 umol/L

- Now what?
Acute management with antihypertensives and magnesium?
### Drugs often used to lower BP acutely in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
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<tbody>
<tr>
<td>Labetalol</td>
<td>20-80 mg</td>
<td>Onset 5 mins</td>
</tr>
<tr>
<td></td>
<td>Max 80 mg (?200mg)</td>
<td></td>
</tr>
<tr>
<td>Nifedipine (oral)</td>
<td>10-20mg tabs</td>
<td>Onset 30-45 mins</td>
</tr>
<tr>
<td></td>
<td>Max 40mg</td>
<td>Repeat 45 mins</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5 -10 mg bolus ivi</td>
<td>Onset 20 mins</td>
</tr>
<tr>
<td></td>
<td>Infusion (5 to max 15mg/hr) after 15-30mg bolus</td>
<td></td>
</tr>
</tbody>
</table>
Acute lowering of BP in Pre-eclampsia

60 women with pre-eclampsia (India)

Initial BP > 160/100

Up to 5 doses 10mg nifedipine
Placebo controlled

1/30 failures nifedipine
5/30 failures labetalol

no maternal hypotension in either group.

Oral Nifedipine or Intravenous Labetalol for Hypertensive Emergency in Pregnancy: A Randomized Controlled Trial.
Shekhar, Shashank; Sharma, Chanderdeep; MD, DNB; Thakur, Sita; Verma, Suresh
Trials evaluating magnesium sulfate for prevention of eclampsia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Magnesium Sulfate n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>No. of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 outcomes for the woman</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal death</td>
<td>11/5400</td>
<td>21/5395</td>
<td>0.54 [0.26, 1.10]</td>
<td>2</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>43/5722</td>
<td>107/5722</td>
<td>0.41 [0.29, 0.58]</td>
<td>6</td>
</tr>
<tr>
<td>Serious morbidity</td>
<td>196/5164</td>
<td>103/5168</td>
<td>1.08 [0.89, 1.32]</td>
<td>2</td>
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<tr>
<td>Renal failure</td>
<td>49/5055</td>
<td>61/5055</td>
<td>0.80 [0.55, 1.17]</td>
<td>1</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>73/5055</td>
<td>86/5055</td>
<td>0.85 [0.62, 1.16]</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>3/5055</td>
<td>6/5055</td>
<td>0.50 [0.13, 2.00]</td>
<td>1</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>3964/5400</td>
<td>4080/5395</td>
<td>0.97 [0.95, 0.99]</td>
<td>2</td>
</tr>
<tr>
<td>Resp depression</td>
<td>52/5344</td>
<td>26/5333</td>
<td>1.98 [1.24, 3.15]</td>
<td>2</td>
</tr>
<tr>
<td>Any side effects</td>
<td>1201/4999</td>
<td>228/4993</td>
<td>5.26 [4.59, 6.03]</td>
<td>1</td>
</tr>
<tr>
<td>Flushing</td>
<td>1032/5066</td>
<td>110/5061</td>
<td>9.38 [7.74, 11.37]</td>
<td>2</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>2520/5082</td>
<td>2370/5026</td>
<td>1.05 [1.01, 1.10]</td>
<td>6</td>
</tr>
<tr>
<td>Blood loss &gt;500 ml</td>
<td>754/4482</td>
<td>775/4427</td>
<td>0.96 [0.88, 1.05]</td>
<td>2</td>
</tr>
<tr>
<td>02 outcomes for the baby</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal/neonatal death</td>
<td>634/5003</td>
<td>611/4958</td>
<td>1.04 [0.93, 1.15]</td>
<td>3</td>
</tr>
<tr>
<td>Death or SCBU &gt;7 days</td>
<td>1330/4538</td>
<td>1302/4486</td>
<td>1.02 [0.95, 1.08]</td>
<td>1</td>
</tr>
<tr>
<td>Intubated at birth</td>
<td>175/4162</td>
<td>171/4098</td>
<td>1.01 [0.82, 1.24]</td>
<td>1</td>
</tr>
<tr>
<td>Admission to SCBU</td>
<td>1629/4162</td>
<td>1591/4098</td>
<td>1.01 [0.96, 1.06]</td>
<td>1</td>
</tr>
</tbody>
</table>

Duley L. *Seminars in Perinatology*  
**Volume 33, Issue 3**, June 2009, Pages 130-137
Should we use Mg for all pre-eclamptics?

1. 500,000 women die per year from pregnancy
   - 10% associated with eclampsia worldwide

2. Rates of eclampsia vary
   - 1 / 2000 – 3700 UK
   - 1 / 100 – 1700 Africa
   - 0.4% cases of Pre-eclampsia at St George hospital
     - Conservative approach – ‘neurological signs’
     - 12% received convulsion prophylaxis
Should we use Mg for all pre-eclampsia?

3. Clear evidence (from MAGPIE) for Mg if Severe Pre-eclampsia:
   - Severe ht; proteinuria > 5g/d; organ dysfunction

4. Costs of preventing one case
   - $21,000 high income country (NNT = 324)
   - $2,500 middle income country (NNT = 184)
   - $450 low income country (NNT = 43)
   - All costs halve if limited to severe PE
Should we use Mg for all pre-eclamptics?

In Australia & NZ limit to:

1. Severe pre-eclampsia, and/or
2. Those with neurological signs
Mrs PE

- Receives oral nifedipine and magnesium bolus then infusion
  - BP 150/100
- Urgent LSCS
- Baby boy 1100g – does well
- Mother – condition resolves over 5 days
Pre-eclampsia continues after delivery
NSAIDs and pre-eclampsia

Postpartum hypertension and nonsteroidal analgesia

Angela Makris, MB, BS,* Charlene Thornton, BN, G. Dip. Mid,
Annemarie Hennessy, MB, BS, PhD
Why doesn’t pre-eclampsia resolve immediately?

- **syncytiotrophoblast Microparticles**
  - expressed in normal pregnancy but more so in PE
  - express high levels tissue factor – procoagulant

- **endothelial and leukocyte Microvesicles higher in PE**
  - higher concentrations of inflammatory and angiogenic proteins

- Are these a major precipitating event or only an epiphenomenon or an amplification?

- Possibly take time to be cleared after delivery
  - ? Sequestered in lungs

Gris. *Hypertension*. 2013; 62: 825-826
What happens after Pre-eclampsia?
Can we predict recurrence of pre-eclampsia or gestational hypertension?


MA Brown, a C Mackenzie, b W Dunsmuir, c L Roberts, d K Ikin, b J Matthews, b
G Mangos, a G Davis d

1515 women with PE or GH; 759 next pregnancies

St George Hospital. Sydney.
Previous preeclampsia: risks of adverse outcomes in subsequent non pre-eclamptic pregnancies

- Swedish cohort (n = 354,676); 1992 through 2006
- 2nd pregnancy; prior preterm preeclampsia:
  - stillbirth, (0.45 vs 0.22%)
  - placental abruption, (0.94 vs 0.32%)
  - preterm births, (5.6 vs 2.5%)
  - SGA <2.5th percentile (4.7 vs 1.2%)
- Term pre-eclampsia increased risk for SGA only

Wikstrom et al. AJOG. Volume 204, Issue 2, February 2011, Pages 148.e1-148.e6
Mrs PE

Wants to know:

1. How can this be prevented next pregnancy?
2. Are there any long term implications?
460 women with Pre-eclampsia (Netherlands); 197 subsequent pregnancy

- Retrospective cohort study
- 40/197 had metabolic syndrome before next pregnancy
- Recurrence of pre-eclampsia
  - 45% vs. 17%
- More components of metabolic syndrome, bigger recurrence risk
  - Esp. hypertension & hyperinsulinemia

- Exercise & weight reduction will help, but..........
  - Other factors appear involved in recurrent pre-eclampsia also

Stekkinger. BJOG. *Volume 120, Issue 8*, pages 979–986, July 2013
Primary outcome — composite recurrent placenta-mediated pregnancy complications (any PE, placental abruption, SGA child [<10th percentile] or pregnancy loss >20 weeks) with LMWH -in women with prior placenta-mediated pregnancy complications (PE, SGA child [<10th percentile], late pregnancy loss [>12 weeks] or placental abruption).

half received aspirin in both groups

(19%) of 358 of women with prophylactic LMWH had recurrent severe placenta-mediated pregnancy complications vs. 127 (43%) of 296 women with no LMWH (p=0.01). Heterogeneity I² = 69%

Long term risks of Pre-eclampsia

1. Fatal & non-fatal IHD
2. Stroke
3. Hypertension
4. Thromboembolism by 5 years
5. Need for a renal biopsy
6. ESKD
7. Diabetes
8. Cognitive dysfunction & WML
8. Death from any cause
Women with pre-eclampsia or GH had greater:

- BMI
- HOMA score
- ABPM measured BP

All results in ‘normal’ range

Mangos GJ, Spaan J, Pirabhahar S, Brown MA
Markers of cardiovascular disease risk after hypertension in pregnancy
Journal of Hypertension 2012, 30:351–358
Where our treatment will be in 10 years
Some possible treatments

1. **Extracorporeal Removal of Soluble Fms-Like Tyrosine Kinase**

2. **VEGF**

3. **Statins**
   - antioxidant, anti-inflammatory, antithrombotic
   - decreasing sFlt-1 levels

4. **Vitamin D**

5. **Eculizumab (C5 inhibitor)**

6. **A1-7 agonists**

7. **AT1RAA antagonists**

8. **ET1 antagonists**
What we’ve discussed

1. **Diagnosing pre-eclampsia is changing**
   - proteinuria in perspective
   - New diagnostic tests?

2. **Determining which women will have poor outcomes**
   - Uric acid remains a useful test

3. **When to deliver and treatment of hypertension**
   - Indications for Mg Sulphate

4. **Pre-eclampsia is more than a disorder of pregnancy**
   - Next pregnancy risks; long term vascular risks

5. Where our treatment might head
International Society for the Study of Hypertension in Pregnancy XIX World Congress

October 24 – 29, 2014

New Orleans, LA, USA