Pre-eclampsia – key issues

James Noblet
The Royal London Hospital
Barts Health NHS Trust
Pre-eclampsia

• Is common – 7.5% pregnancies globally
Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis

Cande V Ananth professor\textsuperscript{1,2}, Katherine M Keyes assistant professor\textsuperscript{2}, Ronald J Wapner professor\textsuperscript{1}

\textsuperscript{1}Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, 622 West 168th Street, New York, NY 10032, USA; \textsuperscript{2}Department of Epidemiology, Joseph L Mailman School of Public Health, Columbia University, New York, NY, USA

• 2-5% of pregnancies in the USA
• Rise of 30% in last decade
Pre-eclampsia

- Is common
- Is rising
<table>
<thead>
<tr>
<th>Cause of death</th>
<th>2009-11</th>
<th>2010-12</th>
<th>2011-13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>All Direct and Indirect deaths</td>
<td>253</td>
<td>10.03</td>
<td>9.36–12.03</td>
</tr>
<tr>
<td>Direct deaths</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sepsis*</td>
<td>15</td>
<td>0.63</td>
<td>0.35–1.04</td>
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<tr>
<td>Pre-eclampsia and eclampsia</td>
<td>10</td>
<td>0.42</td>
<td>0.2–0.77</td>
</tr>
<tr>
<td>Thrombosis and thromboembolism</td>
<td>30</td>
<td>1.26</td>
<td>0.85–1.80</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td>7</td>
<td>0.29</td>
<td>0.12–0.61</td>
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<tr>
<td>Early pregnancy deaths</td>
<td>4</td>
<td>0.17</td>
<td>0.05–0.43</td>
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<tr>
<td>Haemorrhage</td>
<td>14</td>
<td>0.59</td>
<td>0.32–0.99</td>
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<tr>
<td>Anaesthesia</td>
<td>3</td>
<td>0.12</td>
<td>0.03–0.37</td>
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<tr>
<td>All Direct</td>
<td>83</td>
<td>3.49</td>
<td>2.78–4.32</td>
</tr>
<tr>
<td>Indirect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>51</td>
<td>2.14</td>
<td>1.60–2.82</td>
</tr>
<tr>
<td>Indirect Sepsis - Influenza</td>
<td>27</td>
<td>1.13</td>
<td>0.75–1.65</td>
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<tr>
<td>Indirect Sepsis - Pnuemonial/others</td>
<td>16</td>
<td>0.67</td>
<td>0.38–1.09</td>
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<tr>
<td>Other Indirect causes</td>
<td>29</td>
<td>1.22</td>
<td>0.82–1.75</td>
</tr>
<tr>
<td>Indirect neurological conditions</td>
<td>30</td>
<td>1.26</td>
<td>0.85–1.80</td>
</tr>
<tr>
<td>Psychiatric causes</td>
<td>13</td>
<td>0.55</td>
<td>0.29–0.93</td>
</tr>
<tr>
<td>Indirect malignancies</td>
<td>4</td>
<td>0.17</td>
<td>0.06–0.46</td>
</tr>
<tr>
<td>All Indirect</td>
<td>170</td>
<td>7.15</td>
<td>6.11–8.30</td>
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<tr>
<td>Coincidental deaths</td>
<td>23</td>
<td>0.98</td>
<td>0.61–1.45</td>
</tr>
<tr>
<td>Late deaths</td>
<td>325</td>
<td>13.66</td>
<td>12.22–15.33</td>
</tr>
</tbody>
</table>
Pre-eclampsia

- Is common
- Is rising
- Is killing
Placental Ischaemia

At endothelial level

Spiral artery failure

Environmental factors

Genetical factors

Immunological factors

1 & 2nd trimester

Abnormal placentation

3rd trimester

High levels of sflt-1
Low levels of, VEGF, PIGF
Decreased NO
Abnormal vascular health- obesity

Systemic vascular dysfunction

Glomerular endotheliosisis
Proteinuria

Hypertension

Coagulation abnormalities
Loss of blood brain barrier
Eclampsia
Editorial

Hypertension and haemodynamics in pregnant women – is a unified theory for pre-eclampsia possible?

A. T. Dennis
Director of Anaesthesia Research
Staff Specialist Anaesthetist
Department of Anaesthesia
The Royal Women’s Hospital
Parkville
Victoria, Australia
Clinical Associate Professor
Departments of Pharmacology and Obstetrics and Gynaecology
The University of Melbourne
Parkville
Victoria, Australia
Email: alicia.dennis@thewomens.org.au

J. M. Castro
Consultant Cardiologist
Department of Cardiology
St Vincent’s Hospital
Fitzroy
Victoria, Australia
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Hypertension and haemodynamics in pregnant women – is a unified theory for pre-eclampsia possible?
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

- Hypertension
- $\uparrow$C.O / $\uparrow$ SVR / Diastolic Dysfn
- Loss of autoregulation
- Cerebral haemorrhage
- Avoid ergometrine
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

- Headaches
- Nausea & vomiting
- Visual disturbance
- Photophobia
- Clonus + hyperreflexia
- Eclampsia
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

- Fluid Management
- Breathlessness
- Pulmonary Oedema
- Laryngeal Oedema
- Difficult Intubation
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

- Thrombocytopenia
- Haemolysis
- Fibrinolysis
- Coagulopathy
- Thrombosis
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

- Periportal oedema
- Liver enzymes
- Epigastric pain
- Subcapsular haemorrhage
- Rupture
Presentation

- Cardiovascular
- Central Nervous
- Respiratory
- Haematology
- Hepatic
- Renal
- Fetus

• Glomerular endotheliosis
• ↓ Glomerular filtration
• Proteinuria
• ↑ Creatinine / urea
• Acute renal failure
• No NSAIDs
Presentation

• Cardiovascular
• Central Nervous
• Respiratory
• Haematology
• Hepatic
• Renal
• Fetus

• Placental perfusion
• Growth restriction
• Preterm delivery
• Abruption
• Intrauterine death
Definitions & Guidelines

Hypertension in pregnancy: the management of hypertensive disorders during pregnancy

August 2010
NICE Clinical Guideline

HYPERTENSION IN PREGNANCY

Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy

2011  2013  2014
International Guidelines

- Universal emphasis on early diagnosis
- “Mild” pre-eclampsia not described
- Differing approach to proteinuria
- Aspirin prophylaxis for those at risk
NICE 2011

- Hypertension
- Proteinuria
NICE 2011

- Hypertension
- Proteinuria

- New
- After 20 weeks

<table>
<thead>
<tr>
<th></th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>140-149</td>
<td>90-99</td>
</tr>
<tr>
<td>Moderate</td>
<td>150-159</td>
<td>100-109</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;160</td>
<td>&gt;110</td>
</tr>
</tbody>
</table>
NICE 2011

• Hypertension
• Proteinuria

• “Significant”
• Urinary dip of 1+ or more
  - Urinary PCR
  - 24h urine collection
• Significant is:
  - PCR > 30mg/mmol
  - Collection > 300mg protein
NICE 2011

• Hypertension
• Proteinuria
• Severe Pre-eclampsia

• Pre-eclampsia +:
  – severe hypertension
  – and / or symptoms
  – and / or biochemical Δ
  – and / or haematological impairment.
1.1.2 **Antiplatelet agents**

1.1.2.1 Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.
Hypertension in pregnancy (CG107)

1.1.2.2 Advise women with **more than one moderate risk factor** for pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Factors indicating moderate risk are:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m² or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.
Prophylaxis

Calcium supplementation recommended by WHO in women with low dietary calcium

No proven efficacy in
- Oral antioxidants – Vit C & E
- Dietary – salt reduction
- Activity restrictions / bed rest

Heparin?
Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications

Marc A. Rodger,¹ ² Marc Carrier,¹ ² ⁴ Grégoire Le Gal,¹ ² ⁴ Ida Martinelli,⁵ Annalisa Perna,⁶ Évelyne Rey,⁷ J. I. P. de Vries,⁸ and Jean-Christophe Gris,⁹ on behalf of the Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group

¹Hematology, ²Medicine, ³Obstetrics and Gynecology, University of Ottawa and The Ottawa Hospital, Ottawa, ON, Canada; ⁴Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; ⁵Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Internal Medicine and Medical Specialties, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy; ⁶Mario Negri Institute for Pharmacological Research, Clinical Research for Rare Diseases “Aldo e Cele Dacco” Bergamo, Italy; ⁷Centre Hospitalier Universitaire, Ste-Justine Research Center and Obstetrics and Gynecology Department, Department of Medicine, University of Montreal, Montreal, QC, Canada; ⁸Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands; and ⁹Hematology, Clinical Research Unit, University Hospital, Nimes, and University of Montpellier, Montpellier, France

“LMWH may be a promising therapy for recurrent, especially severe, placenta-mediated pregnancy complications, but further research is required.”
Advances in diagnosis

• As yet no predictive test of biomarkers for PET in routine clinical use
• Tests based on PIGF (Placental growth factor) and sFlt-1 (Soluble fms-like tyrosine kinase-1) show most promise
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)

NICE diagnostics guidance [DG23]  Published date: May 2016

Guidance

1 Recommendations

1.1 The Triage PIGF test and the Elecsys immunoassay sFlt-1/PIGF ratio, used with standard clinical assessment and subsequent clinical follow-up, are recommended to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.

- When pre-eclampsia is not ruled-out using a PIGF-based test result, the result should not be used to diagnose (rule-in) pre-eclampsia (see text box).

1.2 The Triage PIGF test and the Elecsys immunoassay sFlt-1/PIGF ratio, used with standard clinical assessment and subsequent clinical follow-up, show promise in helping to diagnose (rule-in) pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. However, there is currently insufficient evidence to recommend their routine adoption for diagnosing pre-eclampsia in the NHS (see text box). Further research is recommended on using these tests in women with suspected pre-eclampsia to rule-in pre-eclampsia (see section 6.2).

1.3 The DELFIA Xpress PIGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PIGF plus Kryptor PE ratio are not recommended for routine adoption in the NHS. Further research by the companies is needed to show the clinical effectiveness of these tests, including diagnostic accuracy and analytical validity.

This guidance only considers using PIGF-based testing to help diagnose suspected pre-eclampsia. NICE is aware of ongoing research linking low PIGF levels and high sFlt-1/PIGF ratios (positive test results) with placental disease, but placental disease is beyond the scope of this guidance. Therefore, the recommendations in this guidance do not consider using PIGF-based testing for conditions other than suspected pre-eclampsia and this guidance is not intended to give advice on diagnosing or managing placental disease. If placental disease is suspected, additional clinical surveillance may be needed (see section 5.10).
PIGF based testing

• “recommended to help **rule-out** pre-eclampsia in women presenting with suspected pre-eclampsia”

• “currently insufficient evidence to recommend their routine adoption for diagnosing pre-eclampsia in the NHS”

• Currently only used for research purposes
Management

- Antenatal issues
- Labour
- Anaesthesia for delivery
- High dependency care
Antenatal - Communication

Must be:
• Senior – consultant level
• Multidisciplinary
• Early

Advocated by:
• NICE
• CEMACH / MBRRACE
• AAGBI / OAA / RCOG
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus

- Rx when mod / severe
- Aim SBP < 150mmHg
- Aim DBP 80-100mmHg
- Oral labetolol 1st line
- Nifedepine / Methyldopa
- IV agents may be needed
- Follow unit protocols
- Cerebral hemorrhage
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus

- Prevent further seizures with Magnesium
- Consider Magnesium for seizure prophylaxis in:
  - “severe” pre-eclampsia
  - in critical care
  - if birth planned in <24h
- If started is normally continued for 24h post del
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus

- Limit fluids to 80ml/h (unless ongoing losses)
- Do not use volume expansion
- Reduce risk of respiratory failure from pulmonary oedema
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus

- No protective therapy against specific glomerular changes
- Most reverse rapidly
- Monitor urine output and renal function
- Post-partum dialysis easier than intra-partum ventilation
End organ protection

• Blood Pressure
• Seizure control
• Fluid balance
• Renal function
• Haematology
• Fetus

• Surveillance
• Trends & absolute values
• Product replacement
• Steroids NOT recommended
• Post partum plasma exchange if HELLP worsening
• Thromboembolic prophylaxis
End organ protection

- Blood Pressure
- Seizure control
- Fluid balance
- Renal function
- Haematology
- Fetus

- Steroids for lungs (24h)
- Fetal Neuroprotection with Magnesium at < 30/42
- Serial growth scans
- Uterine artery flow
Regional analgesia for labour

• Maternal benefit
• Stabilises BP
• Reduces surges
Regional analgesia for labour

- Maternal benefit
- Fetal benefit
- Evidence of increased intervillous blood flow
Regional analgesia for labour

- Maternal benefit
- Fetal benefit
- Contra indications

- Risk of spinal haematoma
- Risk assessment
Coagulation tests

- Platelet count
- Our primary determinant
- Both absolute & relative
- $> 75 \times 10^9 \text{l}^{-1}$
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Normal risk</th>
<th>Increased risk</th>
<th>High risk</th>
<th>Very high risk</th>
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</thead>
<tbody>
<tr>
<td>LMWH – prophylactic dose</td>
<td>&gt; 12 h</td>
<td>6–12 h</td>
<td>&lt; 6 h</td>
<td>&lt; 6 h</td>
</tr>
<tr>
<td>LMWH – therapeutic dose</td>
<td>&gt; 24 h</td>
<td>12–24 h</td>
<td>6–12 h</td>
<td></td>
</tr>
<tr>
<td>UFH – infusion</td>
<td>Stopped &gt; 4 h and APTTR ≤ 1.4</td>
<td></td>
<td></td>
<td>APTTR above normal range</td>
</tr>
<tr>
<td>UFH – prophylactic bolus dose</td>
<td>Last given &gt; 4 h</td>
<td>Last given &lt; 4 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID + aspirin</td>
<td>Without LMWH</td>
<td>With LMWH dose 12–24 h</td>
<td>With LMWH dose &lt; 12 h</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>INR ≤ 1.4</td>
<td>INR 1.4–1.7</td>
<td>INR 1.7–2.0</td>
<td>INR &gt; 2.0</td>
</tr>
<tr>
<td>General anaesthesia*</td>
<td>Starved, not in labour, antacids</td>
<td>Full stomach or in labour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>Platelets &gt; 100 × 10^9.l^{-1} within 6 h of block</td>
<td>Platelets 75–100 × 10^9.l^{-1} (stable) and normal coagulation tests</td>
<td>Platelets 75–100 × 10^9.l^{-1} (decreasing) and normal coagulation tests</td>
<td>Platelets &lt; 75 × 10^9.l^{-1} or abnormal coagulation tests with indices ≥ 1.5 or HELLP syndrome</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia</td>
<td>Platelets &gt; 75 × 10^9.l^{-1} within 24 h of block</td>
<td>Platelets 50–75 × 10^9.l^{-1}</td>
<td>Platelets 20–50 × 10^9.l^{-1}</td>
<td>Platelets &lt; 20 × 10^9.l^{-1}</td>
</tr>
<tr>
<td>Intra-uterine fetal death</td>
<td>FBC and coagulation tests normal within 6 h of block</td>
<td>No clinical problems but no investigation results available</td>
<td></td>
<td>With abruption or overt sepsis</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>INR ≤ 1.4 within 24 h</td>
<td>No other clinical problems but no investigation results available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Coagulation tests

- Platelet count
- Our primary determinant
- Both absolute & relative
- > 75 x $10^9 l^{-1}$
- Risk vs benefit
Coagulation tests

- Platelet count
- Clotting studies

- Late to change
- Routinely performed
- Plt < 100 x 10⁹.l⁻¹
Coagulation tests

- Platelet count
- Clotting studies
- Platelet function

- Aggregation - takes too long
- PFA – detects haemostatic changes
- Visco-elastic – correlates with Plt count
General anaesthesia for C-section

- Airway

- Significant reduction in oro-pharangeal area
- Difficult laryngoscopy/intubation
General anaesthesia for C-section

• Airway
• Blood Pressure

• Surges at intubation & extubation
• Risks intra-cerebral hemorrhage
• Attenuation vital
• Alfentanil 1-2mg
• Remifentanil ~ 1.3 mcg/kg
• Need neonatologists
Regional anaesthesia for C-section

- Historical concern over haemodynamic upset:
  - GA NOT superior to RA
  - Epidural NOT superior to spinal

- More CVS stability in PET vs Normal
  - ↓ Hypotension / ↓ Severity / ↓ Vasopressor
  - Maintenance of vasoconstriction
HDU care & monitoring

Assessment of fluid responsiveness:
• CVP will NOT give you the answer
• Oliguria is to be expected
• Anuria has other causes
• Pulmonary oedema is MUCH worse than AKI
• Fluid restriction is necessary overall
New(er) technology

• Multiple devices to measure CO
  - Pulse waveform analysis
  - Ultrasound / Doppler
  - Electrical resistance

• Application in Obstetric anaesthesia needs further evaluation
Cardiac output monitoring in obstetric anaesthesia

A.T. Dennis
Department of Anaesthesia, The Royal Women’s Hospital
University of Melbourne, Parkville, Australia
E-mail address: Alicia.dennis@thewomens.org.au

R.A. Dyer
Department of Anaesthesia, New Groote Schuur Hospital
University of Cape Town, Cape Town, South Africa

- Cardiac output measurement is essential
- A single monitor and a single number are not enough
- Safe monitoring should yield clinical information that can lead to beneficial changes in care
Pre-eclampsia – key issues

• Important disease
• Pathophysiology → Clinical presentation
• Prevention & early diagnosis
• Principles of management
• Anaesthetic specifics
  ➢ Epidural analgesia
  ➢ C-section anaesthesia
  ➢ Cardiac output monitoring