Pre-eclampsia
A risk factor for pre-term birth, low birth weight and neonatal mortality

Tabassum Firoz MD MSc FRCPC
University of British Columbia
Department of Medicine
Objectives

1. Outline the pathophysiology of pre-eclampsia and its natural history
2. Describe the epidemiology of perinatal morbidity and mortality related to pre-eclampsia
3. Highlight the gaps and identify potential areas for research and action
Pathophysiology of Pre-eclampsia

- Immunological factors:
  - Antigen exposure
    - Primigravidity
    - Primipaternity
    - Donor gamete(s)
    - Duration of cohabitation
    - Barrier contraception
    - Prior miscarriage
    - Smoking

- Genetic factors:
  - Familial risks
  - SNPs
  - Epigenetics

- Lowered threshold:
  - Metabolic syndrome
  - Chronic infection / Inflammation
  - Pre-existing hypertension
  - Chronic kidney disease / DbM
  - High altitude

- Decidual immune cell - EVT interactions:
  - Invasion & uteroplacental artery remodelling

- Inadequate placentation (early-onset pre-eclampsia)

- Uteroplacental mismatch

- Intervillous soup:
  - Pre-eclampsia-specific
    - Placental debris
    - Innate immune activation
    - Oxidative stress
    - Eicosanoids
    - Cytokines
  - Shared with IUGR
    - Angiogenic imbalance

- Endothelial cell activation

- Cardiorespiratory:
  - Hypertension
  - ARDS
  - Pulmonary oedema
  - Cardiomyopathy / LV dysfunction
  - Intravascular volume constriction
  - Generalised oedema

- CNS:
  - Eclampsia
    - TIA / RIND / CVA
    - PRES
    - GCS 13

- Renal:
  - Glomerular endotheliosis
  - Proteinuria
  - ATN
  - AKI

- Hepatic:
  - Periportal inflammation
  - Hepatic dysfunction / failure
  - Hepatic haematoma / rupture

- Haematological:
  - Microangiopathic haemolysis
  - Thrombocytopenia
  - DIC

- Placental IUGR (± maternal syndrome)

- Normal placentation (late-onset pre-eclampsia)
  - Macrosomia
  - Multiple pregnancy
  - ± lowered threshold

- Maternal syndrome
Pre-eclampsia and Feto-placental Implications

<table>
<thead>
<tr>
<th>Adverse conditions</th>
<th>Severe complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Non-reassuring fetal heart rate</td>
<td>o Abruption with evidence of maternal or fetal compromise</td>
</tr>
<tr>
<td>o IUGR</td>
<td>o Reverse ductus venosus A wave</td>
</tr>
<tr>
<td>o Oligohydramnios</td>
<td>o Stillbirth</td>
</tr>
<tr>
<td>o Absent or reversed end-diastolic flow by Doppler velocimetry</td>
<td></td>
</tr>
</tbody>
</table>

Natural History of Pre-eclampsia

- 2 RCTs (133 women) show that expectant care of severe pre-eclampsia was associated with a mean pregnancy prolongation of 2.0 weeks [1.4, 2.6]¹

- A 2009 systematic review found that expectant care of severe preeclampsia <34 weeks (39 cohorts, 4,650 women) was associated with pregnancy prolongation of 7-14 days²

Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy

Laura A. Magee a*, Anouk Pels b, Michael Helewa c, Evelyne Rey d, Peter von Dadelszen a
On behalf of the Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group 1

Severe complications (that warrant delivery)

- Eclampsia
- PRES
- Cortical blindness or retinal detachment
- Glasgow coma scale < 13
- Stroke, TIA, or RIND
- Uncontrolled severe hypertension (over a period of 12hr despite use of three antihypertensive agents).
- Oxygen saturation < 90%, need for ≥ 50% oxygen for > 1hr, intubation (other than for Caesarean section), pulmonary oedema
- Positive inotropic support
- Myocardial ischaemia or infarction
- Platelet count < 50x10^9/L
- Transfusion of any blood product
- Acute kidney injury (creatinine > 150 μM with no prior renal disease)
- New indication for dialysis
- Hepatic dysfunction (INR > 2 in absence of DIC or warfarin)
- Hepatic haematoma or rupture

- Abruptio placentae with evidence of maternal or fetal compromise
- Reverse ductus venosus A wave [85,86]
- Stillbirth
Pre-eclampsia and Perinatal Outcomes

- Spontaneous Pre-term Birth
- Provider Initiated Pre-term Birth
- IUGR (Intrauterine Growth Restriction)
- Low birth weight
- Neonatal death
- Stillbirth
Provider Initiated Pre-term Birth

Hypertension is the leading cause of provider-initiated preterm delivery

- EMIP$^3$: Hypertensive disorders (pre-eclampsia 58.2%, chronic hypertension 15.3%, gestational hypertension 12.9%, and HELLP syndrome 9.4%) were the most common indications of provider initiated pre term delivery

- WHO Multi-Country Survey$^2$: pre-eclampsia (18.2% vs 2.6%, p < 0.001) was higher in women with provider initiated pre-term birth

$^1$ BJOG 121 Suppl: 101–9
$^2$ BMC Pregnancy and Childbirth 2014, 14:56
$^3$ PLoS ONE 11(2): e0148244
Geography of Pre-eclampsia related Pre-term Birth

- Pre-eclampsia rates vary nationally, regionally and globally

- Hypertensive disorders were associated with both spontaneous and indicated preterm birth in all Human Development Index groups

- The risk of preterm delivery caused by these complications did not decrease despite higher levels of country development

<table>
<thead>
<tr>
<th>Maternal condition</th>
<th>All countries (%)***</th>
<th>Very high HDI (%)****</th>
<th>High HDI (%)*****</th>
<th>Medium HDI (%)******</th>
<th>Low HDI (%)*******</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>4077 (1.4)</td>
<td>181 (1.0)</td>
<td>164 (1.7)</td>
<td>208 (1.4)</td>
<td>151 (1.2)</td>
</tr>
<tr>
<td>Infection</td>
<td>458 (0.2)</td>
<td>18 (0.1)</td>
<td>96 (0.1)</td>
<td>235 (0.2)</td>
<td>104 (0.1)</td>
</tr>
<tr>
<td>Puerperal endometritis</td>
<td>270 (0.1)</td>
<td>93 (0.6)</td>
<td>67 (0.1)</td>
<td>58 (0.1)</td>
<td>52 (0.0)</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>966 (0.3)</td>
<td>137 (0.8)</td>
<td>249 (0.4)</td>
<td>355 (0.4)</td>
<td>225 (0.2)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1103 (0.4)</td>
<td>27 (0.2)</td>
<td>86 (0.1)</td>
<td>113 (0.1)</td>
<td>883 (0.8)</td>
</tr>
<tr>
<td>Malaria</td>
<td>372 (0.1)</td>
<td>2 (0.0)</td>
<td>10 (0.0)</td>
<td>52 (0.1)</td>
<td>245 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertensive disorders</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>11188 (0.4)</td>
<td>83 (0.5)</td>
<td>346 (0.4)</td>
<td>446 (0.4)</td>
<td>273 (0.2)</td>
</tr>
<tr>
<td>Pre-eclampsia/edema</td>
<td>7066 (2.4)</td>
<td>445 (2.7)</td>
<td>1908 (2.9)</td>
<td>2841 (2.9)</td>
<td>1902 (0.6)</td>
</tr>
</tbody>
</table>

(B) Adjusted odds ratios and 95% confidence intervals for estimates of effect of maternal medical conditions on preterm delivery

<table>
<thead>
<tr>
<th>Maternal condition</th>
<th>All countries (%)***</th>
<th>Very high HDI (%)****</th>
<th>High HDI (%)*****</th>
<th>Medium HDI (%)******</th>
<th>Low HDI (%)*******</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.5 (1.8; 3.3)**</td>
<td>2.5 (1.8; 3.3)**</td>
<td>1.8 (1.4; 2.5)**</td>
<td>2.3 (1.7; 3.2)**</td>
<td>2.3 (0.92; 5.7)**</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0 (0.9; 1.2)</td>
<td>0.9 (0.9; 1.2)</td>
<td>0.9 (0.9; 1.2)</td>
<td>0.9 (0.9; 1.2)</td>
<td>0.9 (0.9; 1.2)</td>
</tr>
<tr>
<td>Puerperal endometritis</td>
<td>1.6 (1.2; 2.7)</td>
<td>1.6 (1.2; 2.7)</td>
<td>1.6 (1.2; 2.7)</td>
<td>1.6 (1.2; 2.7)</td>
<td>1.6 (1.2; 2.7)</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>2.8 (1.9; 4.1)**</td>
<td>2.8 (1.9; 4.1)**</td>
<td>2.8 (1.9; 4.1)**</td>
<td>2.8 (1.9; 4.1)**</td>
<td>2.8 (1.9; 4.1)**</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.2 (1.0; 1.3)</td>
<td>1.2 (1.0; 1.3)</td>
<td>1.2 (1.0; 1.3)</td>
<td>1.2 (1.0; 1.3)</td>
<td>1.2 (1.0; 1.3)</td>
</tr>
<tr>
<td>Malaria</td>
<td>4.4 (3.2; 6.1)**</td>
<td>4.4 (3.2; 6.1)**</td>
<td>4.4 (3.2; 6.1)**</td>
<td>4.4 (3.2; 6.1)**</td>
<td>4.4 (3.2; 6.1)**</td>
</tr>
</tbody>
</table>

(B) Adjusted odds ratios and 95% confidence intervals for estimates of effect of maternal medical conditions on preterm delivery

<table>
<thead>
<tr>
<th>Hypertensive disorders</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>2.3 (1.9; 2.7)**</td>
<td>3.0 (1.5; 6.0)**</td>
<td>3.3 (2.5; 4.3)**</td>
<td>2.3 (1.8; 2.9)**</td>
<td>1.1 (0.8; 1.7)</td>
</tr>
<tr>
<td>Pre-eclampsia/edema</td>
<td>5.0 (4.7; 5.4)**</td>
<td>5.0 (4.7; 5.4)**</td>
<td>5.0 (4.7; 5.4)**</td>
<td>5.0 (4.7; 5.4)**</td>
<td>5.0 (4.7; 5.4)**</td>
</tr>
</tbody>
</table>

BJOG 2014 Mar;121 Suppl 1:101-9
Pre-eclampsia and Perinatal Death

- 9-20% of perinatal deaths are reported to be a direct result of the hypertensive disorders of pregnancy\(^1\)

- Adverse perinatal outcomes, including stillbirth, are modified by gestational age with the risk of perinatal death being highest at earlier gestational ages\(^1,2,3\)

- Risks of stillbirth and early neonatal death lower in spontaneous preterm deliveries compared with provider-initiated deliveries\(^4\)

\(^1\)FIGO Textbook of the Hypertensive Disorders of Pregnancy
\(^2\)BMC Pregnancy and Childbirth 2014, 14:56
\(^3\)PLoS ONE 11(2): e0148244
\(^4\)BJOG 2014 Mar;121 Suppl 1:101-9
### Chronic Hypertension and Adverse Perinatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of studies</th>
<th>Estimated incidence (%) (95% CI)</th>
<th>Prediction intervals (95%)</th>
<th>Heterogeneity $\tau^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superimposed pre-eclampsia</td>
<td>38</td>
<td>25.9 (21.0 to 31.5)</td>
<td>5.5 to 67.2</td>
<td>0.766</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>27</td>
<td>41.4 (35.5 to 47.7)</td>
<td>15.5 to 73.2</td>
<td>0.413</td>
</tr>
<tr>
<td>Pre-term delivery (&lt;37 weeks)</td>
<td>30</td>
<td>28.1 (22.6 to 34.4)</td>
<td>6.8 to 67.6</td>
<td>0.286</td>
</tr>
<tr>
<td>Birth weight &lt;2500 g</td>
<td>14</td>
<td>16.9 (13.1 to 21.5)</td>
<td>5.7 to 40.6</td>
<td>0.286</td>
</tr>
<tr>
<td>Neonatal intensive care</td>
<td>16</td>
<td>20.5 (15.7 to 26.4)</td>
<td>5.9 to 51.3</td>
<td>0.403</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>27</td>
<td>4.0 (2.9 to 5.4)</td>
<td>0.9 to 16.4</td>
<td>0.544</td>
</tr>
</tbody>
</table>

Bramham et al. BMJ 2014;348:g2301
Summary

- Pre-eclampsia is associated with a number of adverse perinatal outcomes.
- Pre-eclampsia is associated with both spontaneous and provider initiated pre-term birth.
- The spectrum of the hypertensive disorders of pregnancy, particularly chronic hypertension, should be considered for pre-term birth, low birth weight and neonatal mortality.
Discussion: Gaps

- Regional variations: pre-eclampsia prevalence and rates of provider initiated pre-term delivery
- Provider initiated pre-term delivery: exploration of reasons for delivery
- Severe hypertension: optimal and timely management
- Chronic hypertension: pre-conception counseling
- Pre-eclampsia risk modification and surveillance