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

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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
  - Primigravida (♀) / primipaternity (♀)
  - Donor gamete(s) (♀)
  - Duration of cohabitation (♀)
  - Barrier contraception (♀) / fellatio (♀)
  - 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 Placentaion**
- Early-onset pre-eclampsia

**Uteroplacental Mismatch**

**Intervillous Soup**
- Placentaspecific
  - 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**
- Pre-eclampsia
  - TIA / RIND / CVA
  - PRES
  - GCS<13

**Renal**
- Glomerular endotheliosis
- Proteinuria
- ATN
- AKI

**Hepatic**
- Portal inflammation
- Hepatic dysfunction / failure
- Hepatic haematoma / rupture

**Haematological**
- Microangiopathic haemolysis
- Thrombocytopenia
- DIC

**Maternal Syndrome**

**Normal Placentation (late-onset pre-eclampsia)**
- Macrosomia
- Multiple pregnancy
- ± Lowered threshold
## 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 Abruptation 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 days \(^2\)

\(^1\) Obstet Gynecol 1990;76:1070-5; AJOG 1994;171:818-822
\(^2\) Hypertens Pregnancy 2009;28(3):12-47
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 12 hr despite use of three antihypertensive agents)
- Oxygen saturation < 90%, need for ≥ 50% oxygen for > 1 hr, 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 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
  - Low birth weight
- Neonatal death
- Stillbirth

Women’s Medicine Collaborative
A program of The Miriam Hospital
A Lifespan Partner
Provider Initiated Pre-term Birth

Hypertension is the leading cause of provider-initiated preterm delivery\textsuperscript{1,2}

- EMIP\textsuperscript{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\textsuperscript{2}: pre-eclampsia (18.2\% vs 2.6\%, \(p < 0.001\)) was higher in women with provider initiated pre-term birth\textsuperscript{2}

\textsuperscript{1} BJOG 121 Suppl: 101–9
\textsuperscript{2} BMC Pregnancy and Childbirth 2014, 14:56
\textsuperscript{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](image_url)
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>
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