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
  - 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 Placentaion**
- (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 days\(^2\)

\(^1\) Obstet Gynecol 1990;76:1070-5; AJOG 1994;171:818-822

\(^2\) Hypertens Pregnancy 2009;28(312-47.
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 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 < 50x10⁹/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 Low birth weight
- Neonatal death
- Stillbirth

IUGR
Low birth weight
Provider Initiated Pre-term Birth

Hypertension is the leading cause of provider-initiated preterm delivery\(^1,2\)

- 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 preterm 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\(^2\)

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\(^1\) 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.

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

- Adverse perinatal outcomes, including stillbirth, are modified by gestational age with the risk of perinatal death being highest at earlier gestational ages

- Risks of stillbirth and early neonatal death lower in spontaneous preterm deliveries compared with provider-initiated deliveries

1. FIGO Textbook of the Hypertensive Disorders of Pregnancy
2. BMC Pregnancy and Childbirth 2014, 14:56
# 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>
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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