Screening and prevention of preeclampsia

Liona Poon
MBBS MRCOG MD(Res) Cert RCOG (Maternal and Fetal Med)
Associate Professor
The Chinese University of Hong Kong
### Prediction of PE

<table>
<thead>
<tr>
<th>High risk factors</th>
<th>Moderate risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disease in a previous pregnancy</td>
<td>First pregnancy</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>Age ≥ 40 years</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Body mass index ≥ 35 kg/m²</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Inter-pregnancy interval &gt; 10 years</td>
</tr>
<tr>
<td>Autoimmune disease such as SLE or APS</td>
<td>Family history of preeclampsia</td>
</tr>
</tbody>
</table>

#### ACOG 2013: High-risk in need of aspirin
- Preeclampsia in ≥2 previous pregnancies
- Preeclampsia <34w in previous pregnancy

#### NICE: FPR 10.3%
- PE <37w: Detection rate 39%
- PE ≥37w: Detection rate 34%

#### ACOG: FPR 0.2%
- PE <37w: Detection rate 5%
- PE ≥37w: Detection rate 2%
Prediction of PE

Maternal characteristics

- Age (every 5 y above 35)
- Height (every 10 cm)
- Weight (every 10 kg)
- Afro-Caribbean
- South Asian
- Chronic hypertension
- SLE / APS
- In vitro fertilization
- Family history of PE
- Diabetes mellitus
- Parous without PE
- Parous with PE
- Dichorionic twins
- Monochorionic twins

Wright et al. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. AJOG 2015; 213:62
Prediction of PE
Mean arterial pressure

- **Device:** Validated automated devices, calibrated at regular intervals.
- **Method:** Women rested for 5 minutes, arms supported at the level of the heart.
- **Cuff size:** Small (<22 cm), normal (22-32 cm) or large (33-42 cm), depending on the mid-arm circumference.
- **Both arms:** Take average of two measurements in each arm.

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**MAP (MoM)**

Gestational age (w)

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Poon et al. Fetal Diagn Ther 2012
Prediction of PE

Uterine artery PI

Identify the uterine arteries
- Obtain a sagittal section of the cervix and use colour Doppler
- Fixing the probe in the midline then tilt the transducer from side to side to identify the uterine arteries at the level of the internal cervical os

Sampling gate: 2 mm to cover the whole vessel
Angle of insonation: less than 30º
Peak systolic velocity: more than 60 cm/s
Mean PI: average PI (left + right / 2)

1st trimester – transabdominal ultrasound

UTPI (MoM)
Prediction of PE

Angiogenic factors

sVEGFR-1

Anti-angiogenesis

PIGF

Pro-angiogenesis

Gestational age (w)

PLGF (MoM)
Prediction of PE

1st trimester combined test

Maternal risk factors

- Age: every 10 years above 30 y
- Weight: every 10 kg above 70 kg
- Racial origin
  - Afro-Caribbean
  - South Asian
- Obstetric history
  - First pregnancy
  - Previous preeclampsia
- Family history of preeclampsia
- Conception by IVF
- Chronic hypertension
- Diabetes mellitus
- Autoimmune: SLE / APS


Detection rate (%)

- PE <34w: 90%
- PE <37w: 75%
- PE ≥37w: 47%

FPR 10%
### Prediction of PE

#### NICE +ve but FMF -ve

<table>
<thead>
<tr>
<th></th>
<th>High risk factors</th>
<th>Moderate-risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE +ve / FMF +ve</td>
<td>8.7 (6.8-10.9)</td>
<td>4.8 (3.3-6.6)</td>
</tr>
<tr>
<td>NICE +ve / FMF -ve</td>
<td>0.65 (0.2-1.7)</td>
<td>0.42 (0.2-0.9)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.08 (0.03-0.2)</td>
<td>0.09 (0.04-0.2)</td>
</tr>
</tbody>
</table>

34,573 singleton pregnancies at 11-13 w: preterm-PE 239 (0.7%)

In ACOG or NICE +ve women that are FMF -ve the risk of preterm-PE is reduced to within or below background levels

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Prevention of PE

Low-dose aspirin: background

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

Askie et al. Lancet 2007; 369: 1791

• Meta-analysis of individual patient data from 32,217 women in 31 RCTs (24 ASA RCTs)

• RR for PE: 0.90 (95% CI 0.84-0.97)
• RR for birth <34 w: 0.90 (95% CI 0.83-0.98)
**Prevention of PE**

**Low-dose aspirin: background**

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**Gestation at start of aspirin**

<table>
<thead>
<tr>
<th>Gestation</th>
<th>n</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 16 w</td>
<td>1,479</td>
<td>0.47 (0.36-0.62)</td>
</tr>
<tr>
<td>&gt; 16 w</td>
<td>10,673</td>
<td>0.81 (0.63-1.03)</td>
</tr>
</tbody>
</table>

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**In the group with aspirin at <16 w**

<table>
<thead>
<tr>
<th>PE Type</th>
<th>Sample</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term-PE</td>
<td>(37/283 vs 32/273)</td>
<td>0.98 (0.4-2.3)</td>
</tr>
<tr>
<td>Preterm-PE</td>
<td>(2/283 vs 43/273)</td>
<td>0.11 (0.04-0.3)</td>
</tr>
</tbody>
</table>

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Bujold et al., 2010; Roberge et al., 2012; 2013
### ASPRE: Prevention of preterm PE

**Study design**

<table>
<thead>
<tr>
<th>DOSE</th>
<th>150 mg / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>START</td>
<td>11-13 weeks</td>
</tr>
<tr>
<td>FINISH</td>
<td>36 weeks</td>
</tr>
<tr>
<td>TIME</td>
<td>Bed time</td>
</tr>
</tbody>
</table>

- **Aspirin resistance:** 30% at 81mg and 5% at 160 mg
- **Avoid potential hemorrhage for neonate**
- **RCT aspirin 100 mg vs placebo morning, afternoon, night**
- **Aspirin at night: lower incidence of PE, FGR, PTB or IUD**

- **OUTCOME:** Preterm PE
- **STUDY POPULATION:** High-risk group defined by FMF algorithm
Aim
To compare the effects of different doses of aspirin on platelet aggregation and PGI₂ production by vessel wall after ischaemia.

Methods
• 25 young healthy volunteers
• Subjects were allotted to the various dosage groups of aspirin (2, 2.5, 3.5, 5, 8 and 10 mg/Kg).
• PGI₂ production and platelet aggregation were investigated before and after aspirin administration.

Results
• A dose of 2.5 mg/Kg reduced platelet aggregation by 25-35%.
• The inhibition of platelet aggregation was almost at maximum 2h after administration of 3.5 mg/Kg of aspirin. Further increase in the dose (5, 8 and 10 mg/Kg) only provoked a slight increase in inhibition, which was not proportional to the increase in dose.
• PGI₂ production induced by ischaemia was affected by aspirin only at doses higher than 2.5mg/kg.

Average weight 50 Kg = 175 mg/day

Masotti et al, Lancet, 1979
26,941 had screening for PE

High-risk for PE at <37w 2,971 (11%)

Excluded n = 332 (11%)

Eligible for trial 2,641

Declined n = 865 (33%)

Underwent randomization n=1,776

878 assigned to aspirin

898 assigned to placebo

Withdrew consent 152 (8.6%)

Lost to FU 4 (0.2%)

798 analysed

822 analysed

253 Receiving aspirin
47 Hypersensitivity to aspirin
17 Peptic ulcer, bleeding disorders
10 Participation in another drug trial
2 Miscarriage before randomization
3 Termination before randomization

ASPRE: Prevention of preterm PE

Results: effect on rate of PE

ASPRE: Prevention of preterm PE

Results: effect of maternal factors

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Diff in means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of stay in NICU (d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population: admission</td>
<td>N=49</td>
<td>N=54</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td><strong>11.1 (23.4)</strong></td>
<td><strong>31.4 (53.0)</strong></td>
<td><strong>20.3 (7.0-38.6)</strong></td>
</tr>
<tr>
<td>Study population: all cases in the trial</td>
<td>N=798</td>
<td>N=822</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td><strong>0.66 (6.3)</strong></td>
<td><strong>2.06 (15.5)</strong></td>
<td><strong>1.40 (0.45-2.81)</strong></td>
</tr>
<tr>
<td><strong>No. of babies in NICU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population: livebirths</td>
<td>N=777</td>
<td>N=794</td>
<td></td>
</tr>
<tr>
<td>Any, n (%)</td>
<td>48 (6.2)</td>
<td>54 (6.8)</td>
<td><strong>0.94 (0.63-1.42)</strong></td>
</tr>
<tr>
<td>PE</td>
<td>2 (0.3)</td>
<td>18 (2.3)</td>
<td><strong>0.11 (0.02-0.50)</strong></td>
</tr>
<tr>
<td>No PE</td>
<td>46 (5.9)</td>
<td>36 (4.5)</td>
<td><strong>1.38 (0.88-2.15)</strong></td>
</tr>
<tr>
<td>&lt;32w, n (%)</td>
<td>9 (1.2)</td>
<td>23 (2.9)</td>
<td><strong>0.42 (0.19-0.93)</strong></td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>7 (0.9)</td>
<td><strong>0.00 (0.00-0.56)</strong></td>
</tr>
<tr>
<td>No PE</td>
<td>9 (1.2)</td>
<td>16 (2.0)</td>
<td><strong>0.59 (0.26-1.36)</strong></td>
</tr>
<tr>
<td><strong>Length of stay (d)</strong></td>
<td><strong>531</strong></td>
<td><strong>1696</strong></td>
<td></td>
</tr>
</tbody>
</table>
ASPRE: Prevention of preterm PE

Results: potential cost saving

10,000 pregnancies

10% 

1,000 high-risk

No aspirin

Mean NICU stay 2.06d

Total NICU stay 2,060d

Total cost US$8,240,000

Aspirin

Mean NICU stay 0.66d

Total NICU stay 660d

Total cost US$2,640,000

Cost saving US$5,600,000

US$280 per patient screened

Aspirin:

- at a dose of 150 mg per night from 12 to 36 weeks’ gestation reduces the rate of PE <37 w by 62% and PE <34w by 82%
- does not reduce preterm PE in women with CH
- in women without CH the risk of preterm PE is reduced by 95%
- reduces the length of stay in NICU and associated cost by about 70% in pregnancies at high-risk of PE

Thank you