Pre-eclampsia-Eclampsia: an unresolved problem for over 2 millennia

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Training in Reproductive Health Research
Geneva, March 2006
Hypertension in pregnancy

The extent of the problem worldwide
Latin America: Flow Chart

35 countries in America Region

11 countries randomly selected

Argentina, Brazil, Cuba, Ecuador, México, Nicaragua, Paraguay and Perú
(24 geographic units covering the Capital city and 2 randomly selected provinces in each country)

Haiti did not participate

Canada and USA did not started recruitment

410 facilities identified in 23 geographic units
(more than 1000 deliveries/year)

1 Province in Paraguay did not have facilities with more than 1000 deliveries/year

3 facilities refused to participate

123 facilities randomly selected

106546 deliveries during study period
(independent sources)

97095 deliveries recorded
(91% coverage)

120 facilities collected information
4 facilities with restricted recruitment period due to logistic problems.
# Hypertensive disorders of pregnancy

**WHO Global Survey, April 2005**

<table>
<thead>
<tr>
<th></th>
<th>Africa</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of countries randomly selected</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Number of hospitals randomly selected</td>
<td>119</td>
<td>122</td>
</tr>
<tr>
<td>Women surveyed (3 months period)</td>
<td>76,971</td>
<td>97,095</td>
</tr>
<tr>
<td>Preeclampsia (%)</td>
<td>2.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Eclampsia (%)</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension (%) (without proteinuria)</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Chronic hypertension (%)</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Any of above conditions (%)</td>
<td>5.9</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Villar et al, 2005
SCREENING
WHO systematic review of screening for pre-eclampsia

(Conde-Agudelo A, Villar J, Lindheimer MD Obstet and Gynecol 2004;104:1367-1391)
• We considered all cohort or cross-sectional studies of tests to predict preeclampsia

• 7,191 relevant articles → 87 studies included
WHO systematic review of screening for preeclampsia
Abnormal wave form ratio in low-risk women

<table>
<thead>
<tr>
<th>Study</th>
<th>LR pos. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steel . (1990)</td>
<td>5.93 (4.02, 8.74)</td>
</tr>
<tr>
<td>Bewley . (1991)</td>
<td>5.08 (2.74, 9.43)</td>
</tr>
<tr>
<td>Bower (1993)</td>
<td>7.33 (4.88, 11.00)</td>
</tr>
<tr>
<td>North . (1994)</td>
<td>3.38 (2.01, 5.68)</td>
</tr>
<tr>
<td>Frusca . (1997)</td>
<td>6.42 (2.98, 13.85)</td>
</tr>
<tr>
<td>Caforio . (1999)</td>
<td>4.15 (3.50, 4.94)</td>
</tr>
<tr>
<td>Tranquilli . (2000)</td>
<td>1.16 (0.69, 1.96)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>4.24 (3.55, 5.07)</td>
</tr>
</tbody>
</table>

Summary of the review

- There is no clinically useful screening test to predict preeclampsia

- Promising:
  
  Combinations of tests: e.g., plasminogen activator inhibitor [PAI-1/PAI-2] ratio
  + leptin
  + placental growth factor [PIGF])

  Reduced first trimester of PIGF and increases in its soluble inhibitor, fms-like tyrosine kinase (sFlt-1)
Normal Pregnancy

Blood vessel

Vasodilation

Preeclampsia

Sick endothelium

Vasoconstriction

γ FLT-1  ○ VEGF  • PIGF  ○ sFLT-1
sFlt-1: Total citations identified: n = 173

Citations excluded n = 154

Primary articles regarding sFlt-1 and pre-eclampsia n = 19

11 Articles excluded:
Lack of original data, reviews, letters, commentaries, sFlt-1 levels in cord blood, placental samples, samples at PE diagnosis or delivery duplicate data.

Primary articles included in systematic review: n = 8
Circulatory Angiogenic factors and Preeclampsia: sFlt-1

References:
- sFlt-1 significantly increased in women who later developed preeclampsia (PE)
- sFlt-1 did not increase or it did but the difference with the controls was statistically non significant.
PREVENTION
Prevention of pre-eclampsia: Nutrition

- Systematic reviews of R.C.T.s
  - increase protein or energy intake
  - restrict protein or energy for obese women
  - supplementing iron, folate, Mg, Zn, fish oil
  - restricting salt intake
  unlikely to be beneficial

- Promising: Vitamin E and C (one trial completed, 2 ongoing)

- Calcium: WHO trial completed (N = 8,325 women)

WHO Randomized controlled trial of calcium supplementation for the prevention of preeclampsia among low calcium intake women


on behalf of the WHO Calcium Supplementation for the Prevention of Preeclampsia Trial Group (AJOG, 2006)
Study design and patient flow

Baseline nutritional survey at clinic level

Individually clinical screening < 20 weeks of gestation

Randomization

Calcium 1500 mg (day)

Follow up until hospital discharge after delivery

Placebo

Follow up until hospital discharge after delivery

Pre-eclampsia preterm delivery Maternal and perinatal mortality secondary outcomes

Pre-eclampsia Preterm delivery Maternal and perinatal mortality Secondary outcomes
14362 women screened

8788 eligible women

8325 women randomized

4157 Women Calcium Group

4 Not pregnant /2 only trial admission form

143 Lost to follow up - no delivery information (3.4%)

4008 available for analysis of preterm delivery

4151 available for analysis of preeclampsia (at least 1 ANC visit)

4168 Women Placebo Group

5 Not pregnant /2 only trial admission form

155 Lost to follow up - no delivery information (3.7%)

4006 available for analysis of preterm delivery

4161 available for analysis of preeclampsia (at least 1 ANC visit)
Cumulative risk for women in the calcium and placebo groups for pre-eclampsia-eclampsia according to week of gestation.

At 35 weeks ($p = 0.04$).
Cumulative risk for women in the calcium and placebo groups for severe preeclamptic complications according to week of gestation.

(log rank test comparing both curves $p = 0.04$)
# Preterm delivery according to treatment and maternal age

<table>
<thead>
<tr>
<th></th>
<th>Calcium n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 ws)</td>
<td>398/4038</td>
<td>436/4042</td>
<td>0.91</td>
<td>0.79 - 1.05</td>
</tr>
<tr>
<td>Early preterm delivery (&lt;32 ws)</td>
<td>106/4038</td>
<td>130/4042</td>
<td>0.82</td>
<td>0.71 - 0.93</td>
</tr>
<tr>
<td><strong>Women ≤20 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 ws)</td>
<td>148/1400</td>
<td>180/1404</td>
<td>0.82</td>
<td>0.67 - 1.01</td>
</tr>
<tr>
<td>Early preterm delivery (&lt;32 ws)</td>
<td>34/1400</td>
<td>53/1404</td>
<td>0.64</td>
<td>0.42 - 0.98</td>
</tr>
<tr>
<td><strong>Women &gt;20 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 ws)</td>
<td>250/2638</td>
<td>256/2638</td>
<td>0.97</td>
<td>0.83 - 1.15</td>
</tr>
<tr>
<td>Early preterm delivery (&lt;32 ws)</td>
<td>72/2638</td>
<td>77/2638</td>
<td>0.93</td>
<td>0.68 - 1.28</td>
</tr>
</tbody>
</table>

*All risk ratios and 95% Confidence Intervals are adjusted by centre effect.*

*The denominators include multiple births.*
## Severe morbidity and mortality according to treatment group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Calcium n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal admission to intensive care any special care unit</td>
<td>116/4151</td>
<td>138/4161</td>
<td>0.85</td>
<td>0.75 - 0.95</td>
</tr>
<tr>
<td>Maternal admission ≥ 2 days</td>
<td>31/4151</td>
<td>37/4161</td>
<td>0.83</td>
<td>0.57 - 1.21</td>
</tr>
<tr>
<td>Maternal death</td>
<td>1/4151</td>
<td>6/4161</td>
<td>0.17</td>
<td>0.03 - 0.76</td>
</tr>
<tr>
<td>Severe maternal morbidity and mortality index (*)</td>
<td>167/4151</td>
<td>209/4161</td>
<td>0.80</td>
<td>0.70 - 0.91</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>105/4181</td>
<td>113/4197</td>
<td>0.93</td>
<td>0.74 - 1.17</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>37/3953</td>
<td>53/3956</td>
<td>0.70</td>
<td>0.56 - 0.88</td>
</tr>
</tbody>
</table>

(*) At least one of the following: Admission to Intensive Care or any special care unit, eclampsia, severe preeclampsia, placental abruption, HELLP, renal failure or death.

All risk ratios and 95% Confidence Intervals adjusted by centre effect. Maternal outcomes are also adjusted by maternal body mass index.
Cumulative risk of neonatal mortality, by treatment group

Cox regression model
p = 0.02*

Adjusted for clustering on centre
Conclusions

Supplementation with 1.5 gm Ca/day did not reduce the overall incidence of preeclampsia, however it decreased the risk for its more serious complications, including maternal and neonatal morbidity and mortality, as well as preterm delivery among young women.
ETIOLOGY
Are preeclampsia and gestational hypertension different entities?

- Risk Factors
- Pregnancy outcomes


Analyses based on data from the WHO Antenatal Care trial: Lancet 2001 and et al Obstet & Gynecol 2004
Preeclampsia versus Gestational Hypertension

Total Pregnant Population
n = 41751

Abortions
n = 929

Congenital malformation
n = 466

Lost to Follow Up or Not Pregnant
n = 741

Analysis Population
n = 39615

Preeclampsia
n = 874

Reference Group
n = 31273

Gestational Hypertension
n = 2748

IUGR no pre-eclampsia no Gestational HTA
n = 4720
## Risk Factors for Preeclampsia and Gestational Hypertension as compared to the Reference Population

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Preeclampsia (n = 874)</th>
<th>Gestational HTA (n = 2748)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes / Renal / Cardiac</strong></td>
<td>2.4 (1.5 – 3.6)</td>
<td>2.7 (2.1 – 3.5)</td>
</tr>
<tr>
<td><strong>Chronic Respiratory conditions</strong></td>
<td>2.7 (1.2 – 6.5)</td>
<td>0.9 (0.4 – 2.1)</td>
</tr>
<tr>
<td><strong>Pre-eclampsia last Pregnancy</strong></td>
<td>12.7 (10.0 – 16.2)</td>
<td>9.4 (7.8 – 11.2)</td>
</tr>
<tr>
<td><strong>Spontaneous Abortions (&gt; 2)</strong></td>
<td>1.0 (0.7 – 1.5)</td>
<td>1.0 (0.8 – 1.3)</td>
</tr>
<tr>
<td><strong>Urinary Tract Infection</strong></td>
<td>1.4 (1.1 – 1.7)</td>
<td>1.3 (1.2 – 1.5)</td>
</tr>
<tr>
<td><strong>Haemorrhage 1st / 2nd trimester</strong></td>
<td>1.0 (0.6 – 1.5)</td>
<td>1.4 (1.1 – 1.7)</td>
</tr>
<tr>
<td><strong>Reproductive Tract Surgery</strong></td>
<td>1.0 (0.7 – 1.5)</td>
<td>2.2 (1.8 – 2.6)</td>
</tr>
<tr>
<td><strong>Reproductive Tract Infection</strong></td>
<td>0.8 (0.6 – 0.9)</td>
<td>1.3 (1.2 – 1.5)</td>
</tr>
</tbody>
</table>

* Adjusted OR, compared with reference population (n = 31273)
# Risk Factors for Preeclampsia and Gestational Hypertension as compared to the Reference Population

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Preeclampsia (n = 874) OR* (95% CI)</th>
<th>Gestational HTA (n = 2748) OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (&lt; 16 years-old)</td>
<td>1.4 (1.0 – 1.9) ✓</td>
<td>1.3 (1.1 – 1.6) ✓</td>
</tr>
<tr>
<td>Primiparous</td>
<td>2.2 (1.9 – 2.5) ✓</td>
<td>1.2 (1.1 – 1.3)</td>
</tr>
<tr>
<td>Maternal Age (&gt; 40 years-old)</td>
<td>2.8 (1.7 – 4.5) ✓</td>
<td>3.0 (2.4 – 3.9) ✓</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>2.7 (2.3 – 3.2) ✓</td>
<td>2.8 (2.5 – 3.1) ✓</td>
</tr>
<tr>
<td>Low BW in Last Pregnancy</td>
<td>1.3 (0.9 – 1.9)</td>
<td>1.4 (1.1 – 1.7) ✓</td>
</tr>
<tr>
<td>Previous High Weight Babies</td>
<td>0.9 (0.5 – 1.7)</td>
<td>1.7 (1.3 – 2.2) ✓</td>
</tr>
</tbody>
</table>

* Adjusted OR, compared with reference population (n = 31273)
Are they different?

- Preeclampsia: Primiparous; Chronic respiratory conditions?

- Gestational Hypertension: Reproductive pathology, haemorrhage and reproductive infections?
<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n = 874)</th>
<th>Gestational HTA (n = 2748)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Crude</strong></td>
<td>6.0 (5.0 – 7.3)</td>
<td>2.1 (1.7 – 2.4)</td>
</tr>
<tr>
<td>**Adjusted *</td>
<td>1.5 (1.2 – 2.0)</td>
<td>1.2 (1.0 – 1.5)</td>
</tr>
</tbody>
</table>

* OR adjusted by country, treatment, birth weight and socioeconomic status
WHO systematic review of the theories of preeclampsia:

The role of homocysteine

Total citations identified: n = 101

Citations excluded n = 34

Primary articles regarding homocysteine and preeclampsia n = 67

Articles excluded:
- Lack of original data reviews, letters, comments, duplicate data

Primary articles included in systematic review: n = 25
Review of the association between hyperhomocysteinemia and preeclampsia

Follow up Studies

- Sorensen 1999
- Hogg 2000
- Cotter 2001
- Hietala 2001
- Murakami 2001
- Cotter 2003
- Zeeman 2003
- D’Anna 2004

Subtotal (fixed effect model, $P < .001$)

Homocysteine

<table>
<thead>
<tr>
<th>Lower</th>
<th>Higher</th>
<th>WMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.68 [0.40, 0.96]</td>
</tr>
</tbody>
</table>

Test for heterogeneity

$\chi^2 P = .12, I^2 = 38.8\%$

Temporality

Consistency

Strength
# Oxidative stress and endothelial dysfunction among women with and without preeclampsia

## Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Lower in preeclampsia</th>
<th>Higher in preeclampsia</th>
<th>SMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxidative stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powers 1998 (Malondialdehyde, nmol/ml)</td>
<td></td>
<td></td>
<td>0.61 [0.05, 1.17]</td>
</tr>
<tr>
<td>Raijmakers 2000 (Glutathione, µmol/L)</td>
<td></td>
<td></td>
<td>2.00 [1.06, 2.93]</td>
</tr>
<tr>
<td>Raijmakers 2001 (ratio reduced to oxidized glutathione)</td>
<td></td>
<td></td>
<td>0.11 [-0.34, 0.57]</td>
</tr>
<tr>
<td>Tug 2003 (Malondialdehyde, nmol/ml)</td>
<td></td>
<td></td>
<td>5.19 [3.85, 6.54]</td>
</tr>
<tr>
<td><strong>Endothelial dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powers 1998 (Cellular fibronectin, µg/mL)</td>
<td></td>
<td></td>
<td>0.56 [0.00 to 1.11]</td>
</tr>
<tr>
<td>Powers 2001 (Cellular fibronectin, µg/mL)</td>
<td></td>
<td></td>
<td>1.33 [0.69 to 1.97]</td>
</tr>
<tr>
<td>Var 2003 (Nitric oxide, mol/L)</td>
<td></td>
<td></td>
<td>2.53 [1.60, 3.46]</td>
</tr>
</tbody>
</table>
High Levels

↓ Folate
↓ Vitamin B12
MTHFR mutation

↓ Vitamin B6
CBS mutation

Oxidative Stress

Endothelial Dysfunction

Proteinuria - Hypertension

PREECLAMPSIA
Mapping the theories of pre-eclampsia:

The need for systematic reviews of mechanisms of the disease

First, Do the Trials
Then, Do No Harm
By David Brown
Sunday, August 4, 2002;
Page B01, The
Washington Post