Low-dose aspirin & Antioxidants in Prevention of Pre-eclampsia: A literature review

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Introduction

- Pre-eclampsia is ‘The Disease of Theories’
- Classified as PIH
- It occurs in: 2-8 % of all pregnancy
- Characterized: vasoconstriction,
- cell damage and coagulation abnormality
- Maternal mortality/morbidity
Prevention

- Poses greater implication
- Maternal/perinatal outcomes
- Low dose aspirin & antioxidants
- Good results in preventing preeclampsia
- High-risk group of pregnant women
- Prevent unnecessary sequelae
Plan

- Search & Selection Criteria
- Pathophysiology of pre-eclampsia
- Role of low dose aspirin & antioxidants in preventing pre-eclampsia
- The effect of low dose aspirin
- Previous trials of low dose aspirin
- The effect of antioxidants
- Discussion
- Conclusion
Search strategy & selection criteria

- A MEDLINE SEARCH 1980-2000
- Search term: pre-eclampsia, prevention, low dose aspirin and antioxidant
- Manual search of bibliographies
- Ten RCTs
- 18,892 patients
Physiology

- Cell endothelial normal
- Prevent intravascular coagulation by activating protein C
- Produce prostacyclin that inhibites platelete adherence
- Regulate function of thromboxane (vasoconstriction)
Pathophysiology of pre-eclampsia

- Placental ischaemia ----> EC Dysfunction
- Very LDL vs Toxicity-preventing activity
- Immune maladaptation
- Genetic imprinting
- Vasospasm is a basic pathophysiology in PE  (C. Alberd 1918)
Pathophysiology PE

- Vascular constriction
- Resistance in blood flow
- Thromboxan A2 increased
- Vascular sensitive to angiotensin AII
- Inter endothelial cell leaks
Figure I. Pathophysiological hypertensive due to pregnancy
Acetylsalicylic acid (aspirin)

- Most commonly used in the 19th century
- 20-30 billion tablets/year in USA
- Hydrolized to sodium salicyclic acid
- Half-life: 2.7 minutes
- Rapidly absorbed by stomach/ intestine
Aspirin

- Anti platelet drug
- Inhibites cyclooxygenase in pre-systemic (portal) circulation
- Blockes synthesis of thromboxane A2
- Tx A2: vasoconstriction and platelet aggregation
- Dose 1 - 1,6 mg/kg
Action of low dose aspirin

1. Arachidonic acid
2. Cyclooxygenase
   - PGG2
   - PGH2
3. Tx synthetase
4. PGI2 synthetase
   - Thromboxan (platelet)
   - PGI2 (cell endothelial)
Low dose aspirin (60 mg), significantly decreases the production of thromboxan but not PGI 2 in placental arteries
Cyclooxygenase was selectively inhibited with 120 mg aspirin.

97% --> inhibites serum thromboxan B2 & urinary 2.3 dinor thromboxane A2
Previous trials of low dose aspirin in prevention of preeclampsia

- CLASP (Lancet 1994), 9354 women 24-28 weeks of pregnancy, 60 mg/day
- Shift et al. 100 mg/day
- Ylikorkala & Makila 1985, 60 mg/day
- Wallenburg et al. 60 mg/day
- In high risk groups of pregnancy: significant reduction of Pre-eclampsia
# Table I. Trial with high-risk nulliparous subjects.

<table>
<thead>
<tr>
<th>Series</th>
<th>No</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Screening technique</th>
<th>Control</th>
<th>Low-dose aspirin</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallenberg et.al 1986</td>
<td>46</td>
<td>Healthy nulliparous</td>
<td>Hypertension, Renal disease</td>
<td>Angiotensin infusion</td>
<td>30</td>
<td>9</td>
<td>P&lt;0.1</td>
</tr>
<tr>
<td>Shiff et.al 1989</td>
<td>65</td>
<td>Nulliparous, twin gestation, previous pre-eclampsia</td>
<td>Hypertension, proteinuria (+)</td>
<td>ROT</td>
<td>35.5</td>
<td>11.8</td>
<td>P= .024</td>
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<tr>
<td>McParland et al 1990</td>
<td>100</td>
<td>Nulliparous</td>
<td>Diabetes, lupus</td>
<td>Uterine artery doppler scan</td>
<td>19</td>
<td>2</td>
<td>P&lt;.02</td>
</tr>
<tr>
<td>Brown et al, 1990</td>
<td>22</td>
<td>NP +ROT +</td>
<td>Hypertension: diabetes</td>
<td>Angiotensin II infusion</td>
<td>63</td>
<td>27</td>
<td>P&lt;.01</td>
</tr>
<tr>
<td>Wenstrom et al, 1995</td>
<td>48</td>
<td>Nulliparous</td>
<td>Hp: renaldesease, twins, diabetes</td>
<td>HCG&gt;2.0 multiple of the median</td>
<td>10.7</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Bower et al, 1996</td>
<td>60</td>
<td>Any</td>
<td>None</td>
<td>Uterine artery doppler scan</td>
<td>41</td>
<td>29</td>
<td>NS(P=.03)</td>
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</tbody>
</table>

Adapted from Heyborne.KD, AJOG 2000: 183
# High risk with underlying disease

<table>
<thead>
<tr>
<th>Series</th>
<th>No</th>
<th>IC</th>
<th>Control</th>
<th>Incidence of pe Ld asp Ld asp</th>
<th>Sta sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian study 1993</td>
<td>896</td>
<td>Ea, hip, Ppe, tg</td>
<td>2.7</td>
<td>2.9</td>
<td>Ns</td>
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<tr>
<td>CLASP 1994</td>
<td>6929</td>
<td>Ea, hip, crd, ppe, fh, mg, np &amp; dm</td>
<td>6.7</td>
<td>7.6</td>
<td>Ns</td>
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<tr>
<td>EPPA 1996</td>
<td>1900</td>
<td>-</td>
<td>6.7</td>
<td>6.1</td>
<td>Ns</td>
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<tr>
<td>NICD 1998</td>
<td>2539</td>
<td>Ird, hip, crd &amp; mg</td>
<td>22</td>
<td>18</td>
<td>Ns</td>
</tr>
</tbody>
</table>
Effect of anti oxidants in preventing pre-eclampsia

- Free radicals play a part in the genesis
  Robert et al (Lancet 1999)
- Placental ischemia could trigger lipid peroxydation caused endothelial cell damage
- Lipid peroxidase are formed in 2 ways: from free radicals & enzymatic process involving lypooxygenase and cyclo oxygenase
Epidemiological studies

- Countries intake of fruits & vegetables, incidence of coronary heart disease
Oxidative stress

- Lipid peroxidation marker, malondialdehyde & 8 epiprostaglandin F2 increased, antioxidant low in plasma
  Atherosclerosis & preeclampsia
- Vitamin E lipid soluble anti oxidant in LDL
Anti oxidants

- Vitamin E & C
  - ?
- Decrease of oxidative stress
  - ?
- Improvement of vascular endothelial function
  - ?
- Prevention of pre-eclampsia
Cappel et al, Lancet 1999;354:810

- 283 women with highrisk
- abnormal two-stage uterine artery Doppler and previous history
- Vitamin C 1000 mg/day & vit E 400 IU/day or placebo at 16-22 weeks gestation
- significant decrease (21%) PAH1/PAH 2 (CI 95%, p = 0.015)
- PAH-1/PAH-2 ratio reflected endothelial & placental function (no LDL oxidation)
- No detrimental effects on preterm delivery &
Discussion

- The empirical research review show both negative and positive effect of low dose aspirin
- Optimal utilization of screening tools
- No significant perinatal effect
Recommendation: Low dose aspirin to prevent Pre-eclampsia *(AJOG 2000;183)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Low dose aspirin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous, LR</td>
<td>No</td>
<td>Minimal clinical benefit</td>
</tr>
<tr>
<td>Nulliparous, HR</td>
<td>Yes</td>
<td>Group need better screening</td>
</tr>
<tr>
<td>Highrisk, Med</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Highrisk, Obst</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Highrisk, Mul G</td>
<td>Optional</td>
<td>More studies needed</td>
</tr>
</tbody>
</table>
Discussion

- Free radicals promote maternal vascular malfunction
- Wang.Y, reported PE ---> lipid peroxidation in maternal circulation
- Finding mitochondrial (sources of oxygen radicals) fraction increased in placental PE women
- Nitric Oxide (NO) key role maintenance of normal pregnancy
Conclusion

- There were contradictory findings in relation to effectiveness of low dose aspirin in preventing pre-eclampsia in high risk groups of pregnant women
- Future studies should utilize optimal screening tools to identify high risk groups of pregnancy
Conclusion

- Future studies with multicentre trials in larger groups to assess the benefit of antioxidants in preventing pre-eclampsia