PREECLAMPSIA PREVENTION: REVIEW OF GUIDELINES & NEW AREAS OF RESEARCH

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Why prevent preeclampsia?
Objectives

1. Understand current guidelines for preeclampsia prevention.

2. Review studies on the efficacy of low dose aspirin use for preeclampsia prevention.

3. Discuss new areas of research in preeclampsia prevention.
Framework for Presentation

American College of Obstetricians and Gynecologists (ACOG)
2013 Hypertension in Pregnancy Task Force Report

U.S. Preventive Services Task Force (USPSTF)
2014 Recommendation Statement on Low-dose Aspirin in Preeclampsia Prevention

Preeclampsia Definition

ACOG 2013 Guidelines:

• New onset BP $\geq 140/90$ on 2 reads 4hr apart after 20wk GA

and

• Proteinuria
  • $\geq 300$ mg on 24hr urine or
  • P/C ratio $\geq 0.3$mg/dL
  • Dipstick 1+ if other methods NOT available

or

• Severe Features with or without Proteinuria (other than severe range BP)
Preeclampsia with Severe Features

- BP/>=160/110 on 2 reads (4 hours apart on bed rest or spaced minutes apart if antihypertensive initiated before)
- Platelets <100,000
- LFTs 2x normal
- Severe RUQ or epigastric pain persistent and not explained by other Dx
- Cr >1.1 or doubling of baseline Cr without other renal disease
- Pulmonary edema
- New headache or visual changes

ACOG 2013
2013 Preeclampsia Definition Update

- Proteinuria not required
- Massive proteinuria not a severe feature
- IUGR not criteria
- No more “mild” or “severe” preeclampsia
Preeclampsia Background

• Placental dysfunction
• Maternal endothelial dysfunction
• Inflammation
• Prostacyclin-thromboxane imbalance -> vasoconstriction and platelet aggregation
Arachidonic acid

Aspirin — Cyclooxygenase (COX) 1

Prostaglandins $H_2$

Distal enzymes

- In platelets: Thromboxane $A_2$
- In kidney, mucosa, etc.
- In endothelium: Prostacyclin

Prostaglandins like PGI2, PGE2, PGD2

Schramm and Clowse 2014
ACOG 2013 Guidelines

- 60-80mg aspirin daily starting in first trimester for
  - Women with Hx of preeclampsia <34wk
  or
  - Preeclampsia in greater than one prior pregnancy

- No acute risk seen with aspirin
- Long-term fetal effects not known
ACOG 2013 Guidelines

- Calcium supplement in calcium deficient patients
  - Deficiency <600mg/day at baseline
  - Benefit **not** seen in developed countries
ACOG 2013 Guidelines

Unknown/Insufficient Evidence:
• Vitamin D
• Fish oil
• Garlic
• Moderate exercise
ACOG: What doesn’t help
• Vit C or E
• Protein and calorie restriction in obese women
• Salt restriction
• Diuretics
• Bed rest/physical activity restriction
USPSTF Recommendations

• Aspirin 81mg starting at 12-16wk for women at high risk for preeclampsia
  • One high risk criteria – start aspirin
  • Two moderate risk criteria – consider aspirin
  • Grade B evidence
# USPSTF Recommendations Risk Criteria

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
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<tbody>
<tr>
<td>-Hx preeclampsia</td>
<td>-Nulliparity</td>
<td>-Previous uncomplicated term delivery</td>
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<tr>
<td>-Multifetal gestation</td>
<td>-BMI&gt;30</td>
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<tr>
<td>-CHTN</td>
<td>-FHx preeclampsia (1st degree)</td>
<td></td>
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<tr>
<td>-Type 1 or 2 DM</td>
<td>-Sociodemographic (African American, low socioeconomic status)</td>
<td></td>
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<tr>
<td>-Kidney disease</td>
<td>-AMA</td>
<td></td>
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<tr>
<td>-Autoimmune disease</td>
<td>-Personal Hx factor (incl. low birthweight or SGA, previous adverse pregnancy outcome, &gt;10 yr since last pregnancy)</td>
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</table>
Aspirin

- Anti-inflammatory
- Blocks thromboxane synthesis
Efficacy of Low Dose Aspirin

- Mixed conclusions in past
  - Small initial studies show aspirin effective
  - 3 larger RCT did not show significant benefit
  - No major adverse outcomes
Efficacy of Low Dose Aspirin

Cochrane meta-analysis 2007 (updated 2010)

- Anti-platelet agents to prevent preeclampsia
- 37,560 women
- 59 trials (51 studied aspirin alone)

- 17% risk reduction preeclampsia (RR 0.83, 95% CI 0.77-0.89)
Cochrane Meta-analysis 2007

- NNT with antiplatelet agent to prevent preeclampsia
  - 72 women (52, 119)
  - 19 high risk women (13, 34)
  - 119 moderate risk women (73, 333)
Cochrane Meta-analysis 2007

- 8% risk reduction preterm birth (RR 0.92, 95% CI 0.88-0.97)
- 14% risk reduction fetal/newborn/infant death (RR 0.86, 95% CI 0.76-0.98)
- 10% risk reduction small for gestational age births (RR 0.9, 95% CI 0.83-0.98)

Safe

- No significant increased risk abruption, maternal death, C/S, fetal intraventricular hemorrhage or neonatal bleeding

Duley et al. 2007
Cochrane Meta-analysis 2007

Limitations:
- Small trials mostly positive
- Publication bias?

Key areas of future study:
- Exact GA to start aspirin
- Noted higher efficacy with higher doses aspirin – need a study to compare doses

Duley et al. 2007
A closer look at aspirin...

- What gestational age to start aspirin?
- Which guidelines to use to determine preeclampsia risk?
What gestational age to start aspirin?

Roberg et al. 2016

- Meta-analysis of RCTs looking at benefits of aspirin in pregnancy
  - 6 studies, 3 sent data
  - Had to have at least 350 people
  - 11949 participants total; 3293 recruited before 17 wk
  - 60mg aspirin dose, started before or after 17 wk gestation
  - Outcomes: preeclampsia, preeclampsia with SF, SGA
What gestational age to start aspirin?

No difference between starting aspirin before or after 17wk GA
- RR preeclampsia before 17 wk 0.93 (CI 0.75-1.15)
- RR preeclampsia at or after 17wk 0.93 (CI 0.7-1.23)
- Difference between groups p=0.99, not significant

Future study implications:
- Need a large RCT to study further
- Need to study a dose larger than 60mg

Roberg et al. 2016
Which guidelines to use?

Werner et al. 2015

- Attempted to create a decision model based on cost
- Compared 4 protocols of preeclampsia aspirin prevention:
  - No aspirin
  - ACOG guidelines
  - USPSTF guidelines
  - Universal aspirin

- Included cost of aspirin, preeclampsia, preterm birth and adverse outcome of aspirin
- Aspirin started at first prenatal visit and continued until delivery
Which guidelines to use?

<table>
<thead>
<tr>
<th>Approach</th>
<th>Rate of Preeclampsia</th>
<th>% getting Aspirin</th>
<th>$ saved compared to no Aspirin *</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Aspirin</td>
<td>4.18%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>ACOG</td>
<td>4.17%</td>
<td>0.35%</td>
<td>$12 million</td>
</tr>
<tr>
<td>USPSTF</td>
<td>3.83%</td>
<td>23.5%</td>
<td>$377 million</td>
</tr>
<tr>
<td>Universal Aspirin</td>
<td>3.81%</td>
<td>100%</td>
<td>$365 million</td>
</tr>
</tbody>
</table>

*Assumes 4 million births per year.

**USPSTF guidelines:** Similar cost savings to universal aspirin use, ¼ women treated.

Werner et al. 2015
Which guidelines to use?

- USPSTF criteria or universal aspirin prophylaxis – both pragmatic and cost effective
- Recommended USPSTF criteria
  - Similar cost benefit but only ¼ women treated -> less risk
  - Adverse event of GI bleed, abruption, aspirin exacerbated respiratory disease

Werner et al. 2015
New Areas of Research

- Statins
- Metformin
- Enoxaparin
- Exercise
- Vitamin D
- Screening algorithms
Statins in Pregnancy?
Costantíne et al. 2016

• Pravastatin – cat X due to lack of indication rather than documented risk
• Animal preeclampsia models: statins help angiogenic balance and endothelial function.

Costantíne et al. 2016
Statins in Pregnancy?

- Pilot study, first of a series of studies
  - FDA-approved investigational new drug study
  - Collaborated with NICHD

- Double blind placebo controlled RCT focused on safety and pharmakinetics of 10mg pravastatin
- 20 women 12.0-16.6 wk at high preeclampsia risk
- Randomized to daily pravastatin 10mg vs placebo
- Took statin until delivery or a condition developed that required the drug be discontinued

Costantine et al. 2016
Statins in Pregnancy?

- Side Effects: musculoskeletal pain and heartburn
- No myopathy, rhabdo or liver injury
- Reduced maternal cholesterol but not fetal

Costantine et al. 2016
Statins in Pregnancy?

- No maternal, fetal or infant deaths
- No identified safety risks associated with 10mg pravastatin

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<thead>
<tr>
<th></th>
<th>Pravastatin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Preeclampsia</td>
<td>0</td>
<td>4 (3 with SF)</td>
</tr>
<tr>
<td>Preterm del (&lt;37)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Small for GA</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NICU</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Fetal anomalies</td>
<td>Hypospadias</td>
<td>Polydactyly</td>
</tr>
<tr>
<td></td>
<td>Coarctation of the aorta</td>
<td>Ventriculomegaly</td>
</tr>
<tr>
<td>Maternal compl.</td>
<td>none</td>
<td>Postpartum hysterectomy 2/2 to placenta previa and atony</td>
</tr>
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</table>

Costantine et al. 2016
Statins in Pregnancy?

- Promising findings – justifies larger study, dose evaluation
- Potential to be more effective than aspirin
- Follow up with infants planned at 5 yr of age

Costantine et al. 2016
Public Health Significance

Main et al. 2015

• 207 pregnancy related deaths over 2002-2005 in CA
• Preeclampsia/ecclampsia is 2nd leading cause – 17% cases (second to cardiovascular)

• Concluded 60% preeclampsia deaths could have been prevented
• Aspirin prophylaxis can influence maternal death rate (Norton 2016)
Objectives

1. Understand current guidelines for preeclampsia prevention.

2. Review studies on the efficacy of low dose aspirin use for preeclampsia prevention.

3. Discuss new areas of research in preeclampsia prevention.
Conclusions

• Aspirin 81mg daily starting at 12-16wk gestation in *high risk patients*
• Aspirin is safe
• Need further study on long-term impact on childhood development
Conclusions continued

• Calcium supplement benefit in calcium deficient women in developing countries
• New areas of research: statins, metformin, enoxaparin, exercise, vitamin D and screening algorithms.
Why prevent preeclampsia?
Conclusions continued

• Preeclampsia prevention clinical and public health impact: can greatly benefit maternal and infant morbidity and mortality
QUESTIONS?
References
