Strategies for Prescribing Aspirin for Preeclampsia Prevention

March 26, 2021
Should we be prescribing universal low dose aspirin to all pregnant people at 16 weeks?
Objectives

- Epidemiology of preE
- Review pathophysiology of preE
- Aspirin role in preE prevention
- Clinical benefit of aspirin
- USPSTF recommendations
- Review cost analysis
- Conclusions
Why prevention of preE matters

Multisystem inflammatory syndrome with an unclear etiology and natural history

- One of the leading causes of maternal and perinatal morbidity
- Second-leading cause of maternal mortality worldwide

Accounts for 15% of preterm births in the United States
Maternal epidemiology

In 2010, preE affected 3.8% of deliveries in the United States

- Severe preeclampsia has increased over the past 3 decades.
- In the United States, 12% of maternal deaths directly attributable to preeclampsia and eclampsia.
- Morbidity is more common than mortality
- >1/3 of severe obstetric complications are related to preeclampsia
Neonatal epidemiology

Delivery is the only cure for preeclampsia
- Early-onset preeclampsia is usually more severe and often requires preterm delivery.
- Preterm infants (<37 weeks of gestation) are at increased risk for morbidity and mortality
- Complications increase with earlier delivery

Additional important threats to the fetus from preeclampsia include
- FGR
- Placental abruption
- NICU admission
- Neonatal death

Perinatal mortality ~2x higher in pregnancies affected by preeclampsia
Racial disparities in preE

There are racial/ethnic disparities in the prevalence of and mortality from preE

Non-Hispanic black people:
- Are at greater risk for preE than other people
- Bear greater burden of maternal and infant morbidity and perinatal mortality.

In the US, rate of maternal death from preeclampsia is higher in non-Hispanic black people than in non-Hispanic white people

Disparities in risk factors for preeclampsia:
- Limited access to early prenatal care
- Obstetric interventions
- *Toxic stress
- *Provider implicit bias

USPSTF (2014)
Pathophysiology of PreE

**Figure 1.** Pathogenesis of preeclampsia: two-stage model. AT1-AA, autoantibodies to angiotensin receptor 1; COMT, catechol-O-methyltransferase; HTN, hypertension; LFT, liver function test; PIGF1, placental growth factor 1; PRES, posterior reversible encephalopathy syndrome; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase 1; sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor. Reprinted from reference 35, with permission.
Aspirin role in preE prevention

NSAID: Inhibits cyclooxygenase isoenzymes (COX-1 and COX-2), necessary for prostaglandin biosynthesis
- COX-1: present in the vascular endothelium
  - Regulates the production of prostacyclin and thromboxane A
    - Prostacyclin: potent vasodilator and inhibitor of platelet aggregation
    - Thromboxane A (TXA2): potent vasoconstrictor and promotes platelet aggregation
- COX-2: inducible and expressed almost exclusively following exposure to cytokines or other inflammatory mediators
- At lower dosages (60-150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of prostacyclin
- Provides theoretical favorable balance of TXA2 and prostacyclin

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Aspirin role in preE prevention

However, it is likely that preeclampsia arises from poor placentation from a variety of causes:
- Ischemia
- Reperfusion
- Dysfunctional maternal inflammatory response towards the trophoblast

Whether low-dose aspirin improves early placental perfusion is unknown, and likewise, the precise mechanism by which low-dose aspirin acts is poorly understood

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Objectives

- Epidemiology of preeclampsia (PreE)
- Review pathophysiology of preE
- Aspirin role in preE prevention
- **Clinical benefit of aspirin**
- USPSTF recommendations
- Review cost effective analysis
- Conclusions
Magnitude of benefit (and harm): Cochrane Review 2019

77 trials included (40,249 people, and their babies)

**Antiplatelet agents versus placebo/no treatment**

- Reduced **pre-eclampsia** by 18%, number needed to treat for one patient to benefit (NNTB) 61
- Reduced **fetal deaths, neonatal deaths or death before hospital discharge** by 14%; NNTB 197
- Reduced risk of **small-for-gestational age** babies, by 16%, NNTB 146
- Slightly reduced **pregnancies with serious adverse outcome** (a composite outcome including maternal death, baby death, pre-eclampsia, small-for-gestational age, and preterm birth) by 10%, NNTB 54
- Slightly reduced **preterm birth <37 weeks** by 9%, NNTB 61
- Probably slightly increase **postpartum hemorrhage > 500 mL** by 6%, 95% CI 1.00 to 1.12
- Probably marginally increase the risk of **placental abruption** by 21%, 95% CI 0.95 to 1.54

Data from two large trials which assessed children at aged 18 months did not identify clear differences in development
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Factors</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High†</td>
<td>History of preeclampsia, especially when accompanied by an adverse outcome</td>
<td>Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors</td>
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<tr>
<td></td>
<td>Multifetal gestation</td>
<td></td>
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<td></td>
<td>Chronic hypertension</td>
<td></td>
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<td></td>
<td>Type 1 or 2 diabetes</td>
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<td></td>
<td>Renal disease</td>
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<td></td>
<td>Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)</td>
<td></td>
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<tr>
<td>Moderate‡</td>
<td>Nulliparity</td>
<td>Consider low-dose aspirin if the patient has several of these moderate-risk factors§</td>
</tr>
<tr>
<td></td>
<td>Obesity (body mass index &gt;30 kg/m²)</td>
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<td></td>
<td>Family history of preeclampsia (mother or sister)</td>
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<td></td>
<td>Sociodemographic characteristics (African American race, low socioeconomic status)</td>
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<td></td>
<td>Age ≥35 y</td>
<td></td>
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<td></td>
<td>Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, &gt;10-y pregnancy interval)</td>
<td></td>
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<tr>
<td>Low</td>
<td>Previous uncomplicated full-term delivery</td>
<td>Do not recommend low-dose aspirin</td>
</tr>
</tbody>
</table>

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.
† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately ≥8% in a pregnant woman with ≥1 of these risk factors (1, 5).
‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others (1).
§ Moderate-risk factors vary in their association with increased risk for preeclampsia.
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Decision analysis to compare preeclampsia-related costs and effects of four strategies for aspirin use in pregnancy initiated before 16 weeks of gestation to prevent preeclampsia.

1) no aspirin use
2) biomarker and ultrasound measure–predicated use
3) use based on the U.S. Preventive Services Task Force guidelines
4) universal aspirin use.

Outcomes were preeclampsia-related costs and number of cases per 100,000 pregnant people.
Cost benefit balance: preE and LDASA

**No ASA:** 4,234 cases of preeclampsia for every 100,000 pregnant people (4.23%)
- Preeclampsia-associated costs were $38,967,706

**Universal ASA:** Estimated rate of preeclampsia 3.47%
- Compared with no aspirin, $18,750,381 less spent per 100,000 people.

**U.S. Preventive Services Task Force guidelines:** Estimated rate of preE 3.83%
- Increased cost to system (compared to universal) $8,011,725

**Biomarker and ultrasound screening:**
- Increased cost $19,216,551
- 308 additional cases of preeclampsia per 100,000

**Universal ASA cost-effective in 91% of all models**
Cost effectiveness of universal aspirin use

### Table 2. Outcomes and Preeclampsia-Associated Costs of Each Strategy (Per 100,000 Women)

<table>
<thead>
<tr>
<th></th>
<th>No Aspirin</th>
<th>Ultrasound or Biomarker Measures</th>
<th>USPSTF Screen</th>
<th>Universal Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases of preeclampsia</td>
<td>4,234</td>
<td>3,780</td>
<td>3,818</td>
<td>3,472</td>
</tr>
<tr>
<td>Preterm</td>
<td>1,320</td>
<td>829</td>
<td>873</td>
<td>515</td>
</tr>
<tr>
<td>Term</td>
<td>2,914</td>
<td>2,951</td>
<td>2,945</td>
<td>2,957</td>
</tr>
<tr>
<td>Additional cases of preeclampsia</td>
<td>762</td>
<td>308</td>
<td>346</td>
<td>—</td>
</tr>
<tr>
<td>Cases of gastrointestinal bleeding</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Aspirin-exacerbated respiratory disease</td>
<td>0</td>
<td>90</td>
<td>134</td>
<td>480</td>
</tr>
<tr>
<td>Total cost ($)</td>
<td>38,967,706</td>
<td>39,433,876</td>
<td>28,229,050</td>
<td>20,217,325</td>
</tr>
<tr>
<td>Incremental cost ($)</td>
<td>18,750,381</td>
<td>19,216,551</td>
<td>8,011,725</td>
<td>—</td>
</tr>
</tbody>
</table>

USPSTF, U.S. Preventive Services Task Force.
Cost detriment

When is universal ASA not cost effective:

- If aspirin were prescribed, but taken by fewer than 55.2% of pregnant people
- Gastrointestinal bleeding and aspirin-exacerbated respiratory illness:
  - Only at improbably high rates of these complications would universal aspirin not be preferred
  - Ex: If rate of gastrointestinal bleeding was more than 0.94% (est 0.022%)
  - Ex: If the prevalence of aspirin exacerbated respiratory disease was more than 11.8% (est 0.48%)
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Conclusions

- PreE imposes a large public health burden and cost
- Disproportionately affects non-Hispanic black people in the US
- ASA prescription before 16 weeks confers a benefit to pregnant people and their babies
  - Reduces rates of preE
  - Reduces subsequent preterm birth
- Models show cost benefit systemically to universal aspirin prescription
- Patient centered outcomes for universal aspirin prescription need more study
References


ACOG Committee Opinion No 743: Low Dose Aspirin

