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Opinion Article

# Prophylactic Low-Dose Aspirin for the Prevention of Preeclampsia: Are we including all those at risk?

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## Abstract:

**Objective:** Given that preeclampsia is a common adverse pregnancy outcome with an intervention that reduces the rate of early onset preeclampsia by approximately 50% the objective of this review was to review risk factors associated with the development of preeclampsia.
**Methods:** A review of current literature was performed in order to compile the risk for development of preeclampsia with the presence of certain maternal characteristics as well as aberrations in biomarkers.
**Results:** Current literature shows that several biomarkers have a relative risk as high as or higher than the maternal characteristics associated with the development of preeclampsia.
**Conclusions:** Maternal biomarker screening for the development of preeclampsia provide a more inclusive list of patients that should be included in the group receiving aspirin therapy for the prevention of preeclampsia.

## Introduction

Preeclampsia complicates between 2-8% of pregnancies worldwide and accounts for 15% of preterm births in the United States (English F, 2015). In 2018 the Society for Maternal Fetal Medicine (SMFM) and the American College of Obstetrics and Gynecology (ACOG) in a collaborative statement summarized risk factors that should prompt providers to start patients on 81 mg of aspirin per day to prevent the development of preeclampsia (ACOG Committee Opinion No. 743, 2018). These risk factors are shown in Table 1 and are categorized by high and moderate risk. However, there are other risk factors with similar risk for the development of preeclampsia that have been excluded from this list. Our clinical opinion outlines a more inclusive list for aspirin prophylaxis for the prevention of preeclampsia.

## Current Practice:

Aspirin, an irreversible cyclooxygenase-1 inhibitor at low doses, has both anti-inflammatory and antiplatelet effects (ACOG Committee Opinion No. 743, 2018). Several randomized control trials demonstrated the use of low dose aspirin, 81 mg daily, delays the onset and reduces the severity of preeclampsia (Wallenburg HC, 1986; Schiff E, 1989; Rolnik DL, 2017). It has been recommended since 2013 by organizations such as ACOG, SMFM and the USPSTF for the prevention of preeclampsia in at risk women. Patients with one high-risk factor and two low-risk factors should be started on low-dose aspirin between 12-28 weeks' gestation for preeclampsia prophylaxis.

## Results:

Two small trials performed in the late 1980s suggested that low-dose aspirin

may prevent the development of preeclampsia (Wallenburg HC, 1986; Schiff E, 1989). A meta-analysis and Cochrane review also demonstrated that low-dose aspirin reduced the risk of preeclampsia in certain subgroups of patients (Askie LM, 2007; Duley L, 2007). These findings were again confirmed in 2017 when researchers showed that 150-mg of aspirin reduced the risk of preterm preeclampsia (Rolnik DL, 2017). Given these findings in 2018 ACOG and SMFM issued a joint statement recommending low-dose aspirin for the prevention of preeclampsia (ACOG Committee Opinion No. 743, 2018). Outlined in this document were specific clinical risk factors for the development of preeclampsia when aspirin therapy may be of benefit. The relative risk for the development of preeclampsia in these at-risk categories is summarized in Table 2.

| Risk Level | Risk Factors | Recommendation |
|---|---|---|
| High | • History of preeclampsia, especially when accompanied by an adverse outcome<br>• Multifetal gestation<br>• Chronic hypertension<br>• Type 1 or 2 diabetes<br>• Renal disease<br>• Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome) | Recommend low-dose aspirin if the patient has one or more of these high-risk factors |
| Low | • Nulliparity<br>• Obesity (body mass index greater than 30)<br>• Family history of preeclampsia (mother or sister<br>• Sociodemographic characteristics (African American race, low socioeconomic status)<br>• Age 35 years or older<br>• Personal history factors (eg, low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval) | Consider low-dose aspirin if the patient has more than one of these moderate-risk factors |

**Table 1:** Adapted from the 2018 ACOG Committee Opinion shows the high and low risk factors for the development of preeclampsia as well as the recommendation for when to start Aspirin therapy.

These selected risk factors capture many at-risk women. However, they do miss several other at-risk groups. Maternal alpha-fetoprotein is a routinely recommended test drawn between 15-20 weeks gestation to assess the risk of open neural tube defects (Burton BK, 1983). An unexplained elevation in maternal serum concentration is associated with a relative risk of 2.8 for the development of preeclampsia (Wenstrom KD, 1996). A relative risk similar in magnitude to many of the other "high-risk" factors. Uterine artery Doppler velocimetry with the presence of a notch or a resistance index multiple of the median at or above the 75$^{th}$ percentile has a relative risk of 2.2 for the development of preeclampsia (Myatt L, 2012). More recently the imbalance of antiangiogenic (sFlt-1) and angiogenic (PlGF) factors has demonstrated higher risk, up to 5-fold, than most of the high-risk factors outlined by the USPSTF (Veisani Y, 2019). Current Investigators are attempting to use multifactorial screening algorithms to predict the development of preeclampsia. While this approach out performs the clinical diagnosis, the relative risk increase is thought to be small at 1.1-1.2. Table 3 provides the relative risks for additional risk factors for the development of preeclampsia that are not included in the 2018 ACOG Committee Opinion for the initiation of aspirin prophylaxis.

| Risk Factor | Relative Risk |
|---|---|
| History of preeclampsia | 8.4 |
| Chronic hypertension | 5.1 |
| Type 1 or 2 Diabetes | 3.7 |
| Multifetal gestation | 2.9 |
| Obesity | 2.8 |
| Autoimmune disease (SLE, aPLS, etc.) | 2.5-2.8 |
| Nulliparity | 2.1 |
| Renal Disease | 1.8 |

**Table 2:** The relative risk for the development of preeclampsia by risk factor.

| Risk Factor | Relative Risk / Odds Ratio |
|---|---|
| Angiogenic/Antiangiogenic factors (VEGF, PlGF, etc.) | 5.2-2.5 |
| Elevated maternal serum AFP | 2.8 |
| Uterine artery Doppler | 2.2 |
| Multifactorial algorithms | 1.1-1.2 |

**Table 3:** The relative risk or odds ratio for the development of preeclampsia based on the given risk factor.

## Conclusion:

Low dose aspirin is a valuable adjunct therapy that lowers the burden of preeclampsia in our obstetric population and is recommended for use to reduce the risk of its development. The 2018 ACOG Committee Opinion is a useful document in this regard but is limited in scope. Rather than the listing of individual parameters, perhaps as an alternative using relative risk for this adverse condition as a criterion will allow for more flexibility in the decision to use low dose aspirin. This will also permit the inclusion of newly established screening modalities when scientifically proven to be of use. This approach has been endorsed by a recent publication discussing a comprehensive care plan for persons suspected to be at risk for developing preeclampsia (Roberts JM, 2023). The one caution to be taken into consideration is that for each of these risk factors, the pathologic mechanism of action that leads to preeclampsia may differ and therefore ongoing research assessing the benefit of aspirin for each parameter will need to be informative.

**Disclosure Statement:** The authors report no conflicts of interest.

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