Relationship Between Risk Factor Profile and Prescription of Low-Dose Aspirin for Preeclampsia Prevention

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Abstract

Objective:

The purpose of this study was to assess obstetrician-gynecologist utilization of low-dose aspirin for women at increased risk for hypertensive disorders of pregnancy. Further, the study evaluated prescribing practices in relation to specific risk factor profiles in order to identify which women are at highest risk of not receiving recommended therapy.

Methods:

This was a retrospective cohort study reviewed and approved by the local Institutional Review Board. Electronic health records were reviewed to identify risk factors for preeclampsia. Women were eligible for aspirin prophylaxis if they had at least one “high” risk factor or multiple “moderate” risk factors. Associations of interest were addressed using Pearson Chi-squared tests and multinomial logistic regression.

Results:

970 patients were included and 301 women (31%) met criteria for low-dose aspirin prophylaxis; of these, 92 (31%) were given this recommendation. Women eligible for prophylaxis by presence of multiple “moderate” risk factors alone were least likely (0-6%) to have a low-dose aspirin prescription.

Conclusions for Practice:

Low-dose aspirin is an underutilized tool for preventing preeclampsia. Women with a combination of “moderate” risk factors are most likely to not receive indicated aspirin prophylaxis. Efforts should be made to encourage broader uptake of the recommendations for aspirin prophylaxis among obstetrician-gynecologists.

Significance

What is already known on this subject?

Low-dose aspirin has been shown to reduce preeclampsia risk in pregnant women. This preventative measure has been recommended by prominent organizations including the American College of Obstetricians and Gynecologists and the United States Preventive Services Task Force. Yet despite widespread support of this recommendation, uptake is not universal among obstetric care providers.

What this study adds?

This study identifies those who are most likely to experience a missed opportunity for aspirin prophylaxis, thus providing a suggestion for where provider education or other efforts to increase adherence to this guideline may be most impactful.
Introduction

Preeclampsia is a disorder with an estimated annual incidence of 4.6% worldwide. (Abalos et al., 2013) Although affecting less than 5% of patients, this disease and its long-term consequences have a disproportionate impact on pregnancy-related morbidity and mortality. From 2003 to 2009, hypertensive disorders of pregnancy were responsible for 14% of maternal deaths annually – the number two cause of global maternal mortality. (Say et al., 2014) Further, in women affected by preeclampsia, lasting damage to the cardiovascular system likely contributes to morbidity and mortality in future pregnancies and later in life. (Valdiviezo et al., 2012)

The potential complications of preeclampsia during pregnancy are well established and severe, including maternal and fetal death. ("Gestational Hypertension and Preeclampsia," 2020; Mol et al., 2016) Given these potentially devastating consequences, there are ongoing efforts to reduce the risk of developing preeclampsia and mitigate its sequelae. This effort begins with early screening and identification of women at increased risk of preeclampsia or other hypertensive disorders of pregnancy. Various first trimester screening approaches have been proposed, using a combination of historical factors, serum biomarkers, and patient biometric data, however the positive predictive value of these methods remain low at 8-33%. (Espinoza, 2012) The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial utilized a combination approach, assessing historical risk factors, mean arterial pressure, uterine-artery pulsatility index, and serum biomarkers pregnancy-associated plasma protein A (PAPP-A) and placental growth factor. (Rolnik et al., 2017) Using this method, 11% of the 26,941 women screened in the study were deemed high risk for developing preeclampsia and 9% of these high-risk women stratified to the control group ultimately were diagnosed preeclampsia. At this time, in the United States screening is based solely on patient historical factors as outlined by the United States Preventive Services Task Force (USPSTF), (L. LeFevre, 2020) with a goal of identifying women with at least an 8% absolute risk of developing preeclampsia. Such screening should be performed as early in pregnancy as feasible, so as to facilitate preventive measures such as low dose aspirin.

To date, the only tool endorsed by the American College of Obstetricians and Gynecologists (ACOG) for primary prevention of preeclampsia is administration of low-dose aspirin in those women at increased risk of developing the disease. ("Gestational Hypertension and Preeclampsia," 2020) Studies have estimated a 17-24% reduction in the risk of preeclampsia among such women when low-dose aspirin is used. (Askie et al., 2007; Duley et al., 2019; Henderson et al., 2014; Rolnik et al., 2017) Specific dosing continues to be debated as various studies utilizing low-dose aspirin for preeclampsia prophylaxis have used doses ranging 60-150mg/day, with 81mg/day standard dose in the United States and 75mg/day endorsed by the World Health Organization and 150mg/day used routinely by providers around the world. There is a paucity of comparative data to date, and the USPSTF and ACOG only explicitly endorse 81mg/day dosing, citing insufficient evidence to recommend higher dosing.
In 2018 ACOG and the Society for Maternal-Fetal Medicine (SMFM) issued a joint committee opinion advising the prescription of low-dose aspirin at a dose of 81 mg/day, to be initiated between 12 and 28 weeks gestation, to any woman deemed at elevated risk for developing preeclampsia, based on the presence of specific risk factors or combinations of risk factors. ("ACOG Committee Opinion No. 743," 2018) This approach was also given a grade B level of recommendation by the United States Preventive Services Task Force (USPSTF). (L. LeFevre, 2020) According to all three organizations, women are considered eligible for low-dose aspirin prophylaxis if they have at least one “high” risk factor or if they have more than one “moderate” risk factor.

The goal of the current study is to describe the relationship between individual preeclampsia risk factors and aspirin prescribing practices. Secondary outcomes assessed were the development of hypertensive disorders of pregnancy as well as characterization of risk profile (the various combinations of risk factors) and how these relate to aspirin prescribing practices.

**Methods**

This single-site retrospective cohort study was performed at a tertiary care, regional-referral center in the Midwest. The study protocol was reviewed and approved by the Advocate Health Care Network Institutional Review Board (IRB) (Downers Grove, IL). A waiver of informed consent was obtained from the IRB. Data was extracted from the electronic medical record (Epic Systems, Madison WI) of all women ages 18 years and older with singleton gestations, who delivered between February and August of 2020. To improve generalizability of the findings regarding prescribing practices, analysis was restricted to women with singleton gestations. Women fewer than two prenatal visits prior to twenty weeks gestational age (GA) were also excluded in order to ensure that the provider had ample time and opportunity to recommend low-dose aspirin prophylaxis. Additional exclusion criteria were uterine evacuation prior to 20 weeks GA, beta-blocker or calcium channel blocker prescription for non-hypertensive indications, and pregnancy complicated by prenatal diagnosis of a life-limiting fetal condition.

Women were grouped according to their risk of developing preeclampsia, using the classification schema described in ACOG Committee Opinion No. 743: “Low-Dose Aspirin Use in Pregnancy.” ("ACOG Committee Opinion No. 743," 2018) Women were considered at elevated risk, and thus eligible for low-dose aspirin prophylaxis, if they were determined, on retrospective review, to have one or more of the following “high” risk factors: personal history of preeclampsia, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease such as antiphospholipid syndrome or systemic lupus erythematosus; or if they had more than one of the following “moderate” risk factors: nulliparity, obesity defined by body mass index greater than or equal to 30 kg/m$^2$, Black race, or age 35 years or older. Due to the retrospective nature of this analysis the following risk factors were not documented consistently and reliably in the available prenatal records and were thus unable to be assessed: family history of preeclampsia in a first degree relative, low socioeconomic status, history of low birthweight or small for gestational age infant, previous adverse pregnancy outcome, or interpregnancy interval greater than ten years. Additionally, women with
multifetal gestations were excluded in order to identify prescribing trends among the most common patients seen by generalist obstetric providers. Of these, only multifetal gestation is considered a “high” risk factor, the remainder are “moderate” risk factors.

A patient was considered having been prescribed low-dose aspirin if there was mention of the recommendation for low-dose aspirin documented her electronic medical record or if aspirin was included on medication reconciliation at the time of her admission to Labor and Delivery. Specific dosing ranging from 81-162mg/day was left to the individual provider's discretion. Analysis was performed using an intention-to-treat methodology and patient adherence to prescribed therapy was not assessed. Women who met eligibility criteria and who had a low-dose aspirin prescription were classified as having been “appropriately prescribed” whereas eligible women without evidence of an aspirin prescription were deemed “missed opportunities.”

The primary outcome of interest was the rate of “missed opportunities” for aspirin prescription. Secondary outcomes included the specific risk factor profiles corresponding to missed opportunities for prophylaxis, and rates of development of hypertensive disorders of pregnancy among high risk women prescribed and not prescribed low dose aspirin.

Analyses were performed using SPSS (IBM Inc, Armonk, NY). Data are presented as mean ± standard deviation for continuous variables or number (percentage) for categorical variables. All categorical variables were compared using Pearson Chi-square tests and a two-tailed p-value of 0.05 to be considered statistically significant. The association between individual risk factors for preeclampsia and likelihood of low-dose aspirin prescription was addressed using multinomial logistic regression. Results were reported as odds ratios (OR) or adjusted odds ratios (aOR) with 95% confidence interval (CI).

Results

There were a total of 1,138 charts reviewed for study inclusion; of these, 168 patients were excluded, leaving a total of 970 patients included in the analysis. A vast majority [n = 164 (98%)] were excluded due to not having available data from two prenatal visits prior to twenty weeks GA. There was one patient taking propranolol prenatally for portal hypertension and there were three lethal fetal diagnoses. 301 women (31%) were classified as being at increased for developing preeclampsia, and thus were eligible for low-dose aspirin prophylaxis. Of these women, only 92 (31%) were actually prescribed low-dose aspirin (Fig. 1)

This low rate of appropriately prescribed low-dose aspirin was driven primarily by missed opportunities among women who qualified for prophylaxis on the basis of having multiple “moderate” risk factors without comorbid “high” risk factors. There were a total of 179 such women, making up 59% of the population eligible for low-dose aspirin prophylaxis, but only ten (6%) of them were recommended aspirin. These women were 70% less likely to receive indicated low-dose aspirin prophylaxis compared to women
with at least one “high” risk factor (OR 0.3 [95% CI 0.1–0.6], p < 0.001), who were appropriately prescribed low-dose aspirin 67% (n = 82/122) of the time. Table 1 details the rate of low-dose aspirin prescription among women with varying combinations of risk factors.

<table>
<thead>
<tr>
<th>Number of “Moderate” Risk Factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of “High” Risk Factors</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>10/169 (6)</td>
</tr>
<tr>
<td>1</td>
<td>10/17 (59)</td>
<td>33/51 (65)</td>
<td>17/30 (57)</td>
<td>6/8 (75)</td>
</tr>
<tr>
<td>2</td>
<td>1/1 (100)</td>
<td>8/8 (100)</td>
<td>5/5 (100)</td>
<td>2/2 (100)</td>
</tr>
</tbody>
</table>

Data are reported as N (%)

a “Moderate” risk factors include nulliparity, obesity defined by body mass index greater than or equal to 30 kg/m², Black race, or age 35 years or older. “High” risk factors include personal history of preeclampsia, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease such as antiphospholipid syndrome or systemic lupus erythematosus.

Table 1

Figure 2 depicts appropriate prescriptions and missed opportunities, stratified by individual risk factors, among women who were eligible for prophylaxis.

Figure 2

Three of the four “moderate” risk factors studied were associated with a decreased rate of appropriate aspirin prescribing compared to the overall rate. Missed opportunities occurred most frequently in nulliparous women who had at least one additional risk factor, thus qualifying them for preeclampsia prophylaxis. These at-risk women were the least likely to receive an aspirin prescription, at 12% (n = 16/129). Eligible women age 35 years or greater were appropriately prescribed aspirin prophylaxis in 26% (n = 52/199) of cases and 54 of 186 (29%) eligible obese women had a low-dose aspirin prescription. Black race was the only “moderate” risk factor for which aspirin prescription was given at a higher rate [n = 7/13 (54%)] than the overall appropriately prescribed rate.

By contrast, women with the “high” risk factors of diabetes [n = 11/15 (73%)], personal history of hypertensive disorder of pregnancy [n = 52/72 (72%)], chronic hypertension [n = 34/48 (71%)], and autoimmune disorder [n = 1/3 (33%)] were all appropriately prescribed aspirin therapy more often compared to the overall rate of 31%. This is consistent with findings of the multivariate logistic regression model used to determine independent associations between individual risk factors and having a low-dose aspirin prescription (Table 2).
Table 2
Risk factors associated with low-dose aspirin prescription among at-risk women

<table>
<thead>
<tr>
<th>Preeclampsia Risk Factor</th>
<th>No Aspirin Rx (ref) (n = 209)</th>
<th>Aspirin Rx (n = 92)</th>
<th>aOR(^a)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx HDP</td>
<td>20 (10)</td>
<td>52 (57)</td>
<td>34.7</td>
<td>11.4-105.8</td>
<td>&lt; 0.001(^b)</td>
</tr>
<tr>
<td>cHTN</td>
<td>14 (7)</td>
<td>34 (37)</td>
<td>31.5</td>
<td>11.5-86.3</td>
<td>&lt; 0.001(^b)</td>
</tr>
<tr>
<td>Pregestational diabetes</td>
<td>4 (2)</td>
<td>11 (12)</td>
<td>50.7</td>
<td>9.7-264.7</td>
<td>&lt; 0.001(^b)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Autoimmune disease (SLE or APLS)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>10.2</td>
<td>0.76-138.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>113 (54)</td>
<td>16 (17)</td>
<td>0.4</td>
<td>0.14-1.1</td>
<td>0.064</td>
</tr>
<tr>
<td>Obesity</td>
<td>132 (63)</td>
<td>54 (59)</td>
<td>1.6</td>
<td>0.7-3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Black</td>
<td>6 (3)</td>
<td>7 (8)</td>
<td>1.9</td>
<td>0.3-10.9</td>
<td>NS</td>
</tr>
<tr>
<td>AMA</td>
<td>147 (74)</td>
<td>52 (26)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are reported as N (%)
Ref = reference group for odds ratio calculation

According to the model, only the “high” risk factors were independently associated with having an aspirin prescription, a finding that is also intuitive given that, by definition, more than one “moderate” risk factor is required to qualify a patient for prophylaxis, whereas a single “high” risk factor is needed for eligibility.

Table 3 illustrates the impact of aspirin prescription on rates of hypertensive disorders of pregnancy.
Table 3
Hypertensive disorders of pregnancy by aspirin prescription in at-risk women

<table>
<thead>
<tr>
<th></th>
<th>No Aspirin Rx (n = 209)</th>
<th>Aspirin Rx (ref) (n = 92)</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypertensive disorder of pregnancy</td>
<td>163 (78)</td>
<td>59 (64)</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Any hypertensive disorder of pregnancy</td>
<td>46 (22)</td>
<td>33 (36)</td>
<td>0.5 0.3–0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>18 (9)</td>
<td>10 (11)</td>
<td>0.8 0.3–1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Preeclampsia without severe features</td>
<td>12 (6)</td>
<td>6 (7)</td>
<td>0.9 0.3–2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Preeclampsia with severe features</td>
<td>16 (8)</td>
<td>17 (18)</td>
<td>0.4 0.2–0.8</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data are reported as N (%)

Ref = reference group for odds ratio calculation

Abbreviations: Rx = prescription, NS = not significant (p-value ≥ 0.05)

a Statistically significant difference at the level of p < 0.05

Among women deemed at increased risk of developing preeclampsia, in our cohort those who were not prescribed low-dose aspirin appeared to be 50% less likely to develop any hypertensive disorder of pregnancy compared to those who did receive an aspirin prescription (OR 0.5 [95% CI 0.3–0.9], p = 0.013). More specifically, eligible women who did not receive aspirin prophylaxis appeared to have a 60% decreased odds of developing preeclampsia with severe features (OR 0.4 [95% CI 0.2–0.8], p = 0.007).

Conclusions For Practice

Low-dose aspirin prophylaxis is currently the only intervention promoted by the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the United States Preventive Services Task Force for the primary prevention of preeclampsia, a potentially devastating condition for both mother and fetus. The recommendation to prescribe low-dose aspirin to women at elevated risk of preeclampsia was first made by the USPSTF in 2014.(Henderson et al., 2014) And yet, more than six years later, there is little known about the impact of these guidelines on physician prescribing practices. The few studies that have been performed have analyzed only prescription rates among women with the well-recognized “high” risk factors. We are not aware of studies assessing prescribing practices for those women eligible for prophylaxis by multiple “moderate” risk factors. Our
study provides insights into both provider familiarity with identifying women at increased risk for preeclampsia and knowledge of the recommendation to prescribe low-dose aspirin prophylaxis for such women.

One study that examined aspirin prescribing practices, performed by Banala et al., focused on the impact of the ACOG committee opinion recommending aspirin use among women with chronic hypertension. (Banala et al., 2020) The authors found that aspirin was offered to these women at a rate of 7% prior to the publication of the guideline and a rate of 70% following publication. Importantly, the authors found that outcomes of preeclampsia, small for gestational age neonate, and preterm birth were not affected by this change in prescribing practice.

A second study, by Boelig and colleagues, assessed provider adherence to aspirin recommendations before and after implementation of a preeclampsia risk assessment tool designed to help identify at-risk women. (Boelig et al., 2020) The study analyzed only prescribing rates for women with one or more “high” risk factor, and did not assess rates for women with multiple “moderate” risk factors. They found that prior to implementation of the screening tool 74% of eligible women were recommended aspirin prophylaxis, compared to 95% following this intervention.

Unlike prior analyses, our study considered both “high” and “moderate” risk factors when determining which patients ought to have been prescribed low-dose aspirin prophylaxis. We found that up to 69% of women deemed at-risk for preeclampsia by the ACOG, SMFM, and USPSTF guidelines were not given a recommendation for aspirin prophylaxis. Despite having the same risk for developing preeclampsia as women with a single “high” risk factor, women who qualified for aspirin prophylaxis solely on the basis of having multiple “moderate” risk factors were significantly less likely to be prescribed low-dose aspirin. But even among women with a single “high” risk factor, aspirin was prescribed at best 75% of the time. The improved prescription rate among women with “high” risk factors may be due to greater recognition of the association between those factors, such as history of preeclampsia or chronic hypertension, and the risk of developing preeclampsia. Another potential explanation is that these women are perhaps more likely to be referred to Maternal-Fetal Medicine specialists, who may be more familiar with the guidelines and more comfortable recommending aspirin therapy.

One curious finding that deserves additional explanation is the apparent reduction in risk of preeclampsia or gestational hypertension and of preeclampsia with severe features in women not taking aspirin. The authors feel that this is not so much a finding refuting the benefits of low-dose aspirin, but rather highlighting the observation that only the women at very highest risk of developing preeclampsia – those with two or more “high risk” factors – were the only ones reliably prescribed aspirin in our cohort. Thus, the finding is interesting and worth noting for completeness, however is not thought to be an accurate representation of the effectiveness of low-dose aspirin.

This study is limited by the retrospective nature of its analysis. Because of this, not all preeclampsia risk factors were able to be reliably assessed when classifying patients and determining their eligibility for aspirin prophylaxis. The impact of these missing risk factors can be estimated and accounted for by the
observation that there were 16/669 “low risk” women who received an aspirin prescription. All “high-risk” risk factors were assessed in this group ultimately determined to not be candidates for aspirin prophylaxis by the factors examined in this study, so these sixteen women were either prescribed low-dose aspirin for indications beyond the specific recommendations of ACOG and the USPSTF, or they could theoretically have been identified through possessing two or more of the “moderate-risk” risk factors unable to be assessed in this study. Even if all sixteen of these women did truly meet criteria for low dose aspirin, the key finding of this study that women with multiple “moderate-risk” risk factors are often overlooked as candidates for preeclampsia prophylaxis would remain as the proportion of women without any “high-risk” risk factors who received an indicated low dose aspirin prescription would still be only 26/195 (13%) versus 82/122 (67%) among women with at least one “high-risk” risk factor. Thus, we believe the results of this study are still meaningful because expanding the review to include additional risk factors would only increase the number of eligible women, and thus would likely only enhance our current findings.

These findings indicate a need for further education among generalist obstetrician-gynecologists about screening women for risk factors associated with preeclampsia, with a focus on identifying women with multiple “moderate” risk factors. Prospective studies specifically designed to assess aspirin utilization practices are needed in order to completely define the problem and identify the most critical areas for improvement. Future studies that seek to understand factors motivating prescriber practices will also be important in order to inform interventions aimed at increasing uptake of low-dose aspirin for preeclampsia prophylaxis. Finally, it is critical to study the impact of these efforts on the outcome of interest—preeclampsia and its sequelae—to determine the clinical consequences of fully implementing these guidelines and to assess real-world efficacy of preeclampsia risk factor screening and low-dose aspirin prophylaxis.

**Abbreviations**

Rx
prescription
Hx HDP
history of hypertensive disorder of pregnancy
CHTN
chronic hypertension
SLE
systemic lupus erythematosus
APS
antiphospholipid syndrome
AMA
advanced maternal age (age 35 years or older)
NS
not significant (p-value ≥ 0.05)
Declarations

Funding: There was no financial support obtained for the conduct of this research or preparation of this article for publication.

Conflicts of interest: The authors report no conflicts of interest.

Ethics approval: The project was reviewed and approved by the local Institutional Review Board (IRB) prior to commencement of the project.

Consents: Waivers of informed consent or consent for publication were obtained from the IRB due to the retrospective nature of this chart review and since no patient-identifying information will be published.

Data transparency: Data was obtained from the local electronic medical record, inquiries regarding data can be directed to the corresponding author.

Authors’ contributions:

Alexandra Phelps: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft

Calla Holmgren: Conceptualization, Writing – Review & Editing, Supervision

References


Figures

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Figure 1

Study population, preeclampsia risk classification, and aspirin prescription

This figure illustrates study selection criteria and breakdown of preeclampsia risk classification and aspirin prescription.
Figure 2

Low-dose aspirin prescriptions among eligible women, by risk factor

Bar graph depicting the percentages of appropriately prescribed aspirin and missed opportunities, by individual preeclampsia risk factor.

Abbreviations: Hx HDP = history of hypertensive disorder of pregnancy, CHTN = chronic hypertension, AA = African-American (Black race), SLE = systemic lupus erythematosus, APS = antiphospholipid syndrome, AMA = advanced maternal age (age 35 years or older)