Best Practice Alert (BPA) for Low Dose Aspirin Recommendation in High-Risk Pregnancies: a Randomized Controlled Trial

Study Protocol with Statistical Analysis Plan

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Study Protocol

Scientific Background

Preeclampsia is a significant cause of maternal morbidity and mortality, affecting up to 8% of pregnancies worldwide. Low dose aspirin (LDA) has been found to reduce the incidence of preeclampsia in high-risk pregnant patients.

Objectives

Upon internal review of electronic health record (EHR) data at our institution, we found that the recommendation for LDA use in high-risk pregnant patients was 60%. We hypothesize that the implementation of the EHR Best Practice Alert (BPA) will increase the healthcare provider's recommendation for LDA compared to the current standard care.

Design

We propose an RCT to assess the effect of an EHR clinical decision support (CDS) tool, specifically a BPA, on healthcare provider recommendations for low dose aspirin in high-risk pregnant patients.

Methods

Pregnant patients who receive and initiate prenatal care within Geisinger prior to 28 weeks gestation will be included if they are considered at high-risk of preeclampsia based on the modified United States Preventive Services Task Force (USPSTF) and American College of Obstetrics and Gynecology (ACOG) criteria listed above. Eligible patients will be randomized in a 1:1 fashion to a control or experimental group. In the control group, the women's health care provider will not receive a BPA; the pregnancy management will be based on the healthcare provider's current practice and knowledge. In the experimental group, the women's health care provider will receive a BPA in the EHR noting that the patient is at high-risk for preeclampsia and that the provider should recommend LDA. If LDA is not recommended, there will be a required acknowledgment reason from the provider noting a rationale for not initiating LDA. We defined women's health care provider as one of the following obstetric care providers who are able to prescribe medications: physicians (including resident physicians), physician assistants, certified registered nurse practitioners, and/or certified nurse midwives. Maternal-Fetal Medicine visits are excluded.

In the experimental group, when the BPA fires, the provider can either accept the BPA recommendations (to prescribe LDA and to add this medication to the medication list) OR the provider can reject the BPA. If the BPA is rejected, the provider must choose a reason for rejection, i.e., patient declined, patient allergic to aspirin, patient taking aspirin, patient does not meet ACOG criteria for LDA, and Other (with comment). These specific rejection reasons will be reviewed by study team members on an on-going basis, so that the algorithm can be updated if needed to ensure it is only applying to those patients for whom LDA should be recommended.

Power Analysis

A total of 640 patients will be required to yield an adequate power to show a statistically significant difference in LDA recommendation rate. However, we plan to enroll an additional 10% to account for possible early miscarriags and early terminations.

Project Status

Patients will be randomized to study arms as they showed up to their appointments with an anticipated start date of June 19, 2023. Data collection is ongoing until the primary outcome date of June 19, 2025 (after the conclusion of pregnancy for all enrolled patients).

Statistical Analysis Plan
Planned Analyses

Primary Outcome: *A sensitivity analysis of the healthcare provider recommendation for low dose aspirin use in patients, specifically those who deliver after 28 weeks*
[Time Frame: Assessed between initial prenatal visit and delivery after 28 weeks]

Outcome Description: Patient chart indicates that the provider recommended aspirin (yes/no) between the day of the initial prenatal visit and delivery (≥ 28 weeks). The outcome is captured either by aspirin being added to the patient's medication record or via a prespecified algorithm searching notes for text strings such as "LDA," "ASA," "baby aspirin," etc. As per ACOG, low dose aspirin therapy should be initiated between 12 and 28 weeks, therefore we limited this outcome to patients who deliver after 28 weeks to ensure the provider had the entire window that ACOG allows to make the recommendation for low dose aspirin initation.

Question: Does a BPA, which identifies patients as HRPP and recommends and facilitates LDA prescribing, that fires during prenatal visits increase the likelihood of LDA recommendation/prescribing in comparison with no BPA firing?

Secondary Outcome: *The healthcare provider recommendation for low dose aspirin use in all randomized patients [Time Frame: Assessed between initial prenatal visit and conclusion of pregnancy]*

Outcome Description: Patient chart indicates that the provider recommended aspirin (yes/no) between the day of the initial prenatal visit and delivery (or conclusion of pregnancy). The outcome is captured either by aspirin being added to the patient's medication record or via a prespecified algorithm searching notes for text strings such as "LDA," "ASA," "baby aspirin," etc. This outcome will take into consideration all patients randomized, including those whose pregnancies resulted in termination, miscarriage or preterm delivery prior to 28 weeks. This intention-to-treat outcome will help assess the effect of the BPA in all patients.

Other pre-specified outcome measures
Outcome 1: *Patient taking low dose aspirin [Time Frame: Assessed at time of delivery (≥ 28 weeks)]*

Outcome Description: Patient chart indicates that the patient took aspirin (yes/no) during the pregnancy and up until delivery (≥ 28 weeks). The outcome is captured by aspirin being on the qualifying patient's medication record.

Outcome 2: *Rate of preeclampsia [Time Frame: Assessed at time of delivery]*

Outcome Description: Patient chart indicates that the patient experienced preeclampsia (yes/no) during the pregnancy, up until delivery. The outcome will be assessed at two time points, ≥ 28 weeks (so that patients were allowed the full window for low dose aspirin initiation) and ≥ 20 weeks (excluding miscarriages and earlier terminations of pregnancy). The outcome is captured by a diagnosis of preeclampsia on the qualifying patient's chart noted either by chart review or an algorithm that was created to capture this diagnosis.

Outcome 3: *Timing of low dose aspirin recommendation [Assessed between initial prenatal visit to delivery (≥ 28 weeks)]*

Outcome Description: Gestational age (in weeks) at the time that aspirin was first recommended (as indicated in the patient chart) between the day of the initial prenatal visit and delivery (≥ 28 weeks).

Outcome 4: *Timing of low dose aspirin initiation [Assessed between initial prenatal visit to delivery (≥ 28 weeks)]*

Outcome Description: Gestational age (in weeks) at the time that aspirin was initiated (as indicated in the patient chart) between the day of the initial prenatal visit and delivery (≥ 28 weeks

Outcome 5: *Preterm delivery [Time Frame: Assessed at delivery]*

Outcome Description: Patient chart indicates that the patient experienced a preterm delivery (yes/no) during the pregnancy. The outcome will be assessed at two time points, ≥ 28 weeks (so that patients were allowed the full window for low dose aspirin initiation) and ≥ 20 weeks (excluding miscarriages and earlier terminations of pregnancy). The outcome is captured by a diagnosis of preterm delivery on the qualifying patient's chart noted either by chart review or an algorithm that was created to capture this diagnosis.

Outcome 6: *Provider response to best practice alert [Time Frame: Assessed between initiation prenatal visit to delivery (≥ 28 weeks)]*

Outcome Description: Data from the best practice alert will inform the study team of which responses are selected by the provider when responding to the best practice alert. Selection of prespecified responses by the provider will be reviewed on a weekly basis during the study period to assess whether the best practice alert triggering criteria needs to be adjusted.

Outcome 7: *Number of times the best practice alert fired for a patient [Time Frame: Assessed between initial prenatal visit to delivery (≥ 28 weeks)]*

Outcome Description: The BPA will stop firing once the BPA has been successfully addressed. Data from the BPA will inform the study team the number of times the BPA fired for a qualifying patient.

Analysis Notes

Recent work suggests that OLS regressions are appropriate in randomized experiments with binary outcome variables such as ours (Gomila, 2021).

Each analysis for the specified outcomes will be run using an OLS regression to examine whether the outcome differs as a function of experimental arm. For all analyses, if the distribution for a continuous outcome is positively skewed, a negative binomial or other appropriate model may be used instead.

As the treatment variation is at the individual level, we will report heteroskedasticity-robust standard errors. We will also explore the impact of clustering these standard errors at the clinic and clinic-date levels to allow for dependence across observations within these clusters. We will also investigate heterogeneity across clinics that vary along characteristics of interest, including prior-year recommendation rates.

References:

1. Gomila, R. (2021). Logistic or linear? Estimating causal effects of experimental treatments on binary outcomes using regression analysis. *Journal of Experimental Psychology: General*, *150*(4), 700-709. https://doi.org/10.1037/xge0000920
2. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. U.S. Preventive Service Task Force. Ann Intern Med 2014; 161: 819 – 26.
3. ACOG Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy. *Obstet Gynecol*. 2018;132(1):e44-e52. doi:10.1097/AOG.0000000000002708