DUHS IRB Application (Version 1.6)

Approval Date: 05/01/2024
NCT05889468

General Information

*Please enter the full title of your protocol:		
The association between postpartum aspirin use and NT-proBNP levels as a marker for maternal health outcomes: a randomized-controlled trial		
***Please enter the Short Title you would like to use to reference the study:**		
Postpartum ASA and NT-proBNP * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

Specific Aim 1: To compare NT-proBNP levels at 4-6 weeks postpartum between patients continued on 6 weeks of aspirin use postpartum and placebo.
Our hypothesis is that NT-proBNP levels will be lower in the group randomized to continuation of aspirin for 6 weeks' postpartum. As we know that aspirin use during pregnancy decreases preeclampsia risk and that preeclampsia in itself is a risk factor for long-term cardiovascular disease in our patient population, we anticipate that the continuation of aspirin in the postpartum setting decreases cardiac strain and that patients continued on maintenance aspirin dosing will have lower NT-proBNP levels at 4-6 weeks postpartum.

Specific Aim 2: To compare average blood pressure readings at the 4-6 week postpartum visits as well as hospital readmission rates for blood pressure monitoring or cardiovascular concerns in the 4-6 week postpartum period between groups.
We plan to evaluate if patients continued on aspirin for 6 weeks postpartum have lower hospital readmission rates than patients on placebo. This could support prior data that showed that prenatal aspirin use was associated with decreased incidence of postpartum hypertension following delivery and decreased rates of hospital readmission.

Background & Significance

- Should support the scientific aims of the research

Preeclampsia is a hypertensive disorder of pregnancy that affects 2-8% of all pregnancies and is a leading cause of maternal and neonatal morbidity and mortality worldwide.[1-2] Maternal complications associated with preeclampsia include stroke, seizure, permanent end organ damage, and maternal death. Importantly, preeclampsia is also a defined risk factor for future cardiovascular morbidity and mortality and has been associated with increased long-term risk of chronic hypertension, cardiovascular disease, and death.[3-4] Neonatal complications include preterm delivery and associated complications, intrauterine growth restriction, placental abruption, and intrauterine fetal demise.[1] While the exact etiology of preeclampsia is unknown, prior studies have suggested the imbalance in prostacyclin and thromboxane A2 (TXA2) metabolism as a contributing factor. [5-6] For this reason, aspirin was targeted as potential intervention for the prevention of preeclampsia.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that acts primarily on cyclooxygenase isoenzymes 1 and 2 (COX-1 and COX-2) to regulate prostacyclin production. At lower doses (60-150 mg /day), ASA selectively acts on COX-1, thereby inhibiting TXA2 secretion without affecting the secretion of endothelial prostacyclin.[7-8] This results in a vasodilatory effect and in the reduction of platelet aggregation, which is thought to improve placental perfusion and decrease the incidence of preeclampsia.[9] ASA has also been recommended by the USPSTF as primary prevention of cardiovascular disease in at-risk individuals 40-59 years of age as well as secondary prevention in survivors of cardiovascular occlusive events.[10]

Interventions aimed to reduce the incidence of preeclampsia are paramount to public health given the short- and long-term implications associated with the diagnosis. Unfortunately, hospital admission rates involving a diagnosis of a hypertensive disorder are increasing and have been associated with higher rates of acute renal failure, disseminated intravascular coagulation syndrome, pulmonary edema, cerebrovascular disorders, and overall maternal morbidity and mortality.[11] Additioally, a systematic review and meta-analysis by Wu et al evaluated future risk of cardiovascular disease in patients diagnosed with preeclampsia during pregnancy and found that preeclampsia was associated with a 4-fold increase in the incidence of future heart failure and a 2-fold increase in incidence of coronary artery disease, cerebrovascular accidents, and death.[12] The American Heart Association now considers a history of preeclampsia a risk factor for development of future cardiovascular disease and targets these populations as "at risk" individuals who may benefit from lifestyle modifications to lower their risk of heart disease.[13]Fo r this reason, annual medical reviews are recommended life-long for patients with a history of preeclampsia, and further research is needed into prevention to decrease maternal morbidity and mortality.[14]

Administration of low-dose aspirin has been demonstrated to decrease the risk of development of preeclampsia in high-risk patients, defined by the National Institute for Health and Care Excellence (NICE) guidelines as any patient with a history of hypertensive disorders of pregnancy, chronic kidney disease, autoimmune disease, chronic hypertension, first pregnancy, age >40 years, pregnancy interval >10 years, BMI>35, multiple gestation, or family history of preeclampsia.[15] For this reason, both the USPSTF and the WHO recommend administration of low dose aspirin in patients with one high risk or multiple moderate risk factors for preeclampsia.[16-17] Initiation of aspirin is recommended between 12 and 28 weeks, ideally before 16 weeks, as a recent meta-analysis demonstrated only a modest reduction in preeclampsia when aspirin was started after 16 weeks but a significant reduction in preeclampsia and intrauterine growth restriction if initiated before this gestational age.[18] ACOG recommends continuation of aspirin until delivery.[1]

A recent study by Christenson et al studying patients with preeclampsia on aspirin prevention found that prenatal aspirin use was associated with a decreased incidence of postpartum hypertension within 48 hours after delivery and decreased rates of 6-week hospital readmission.[19] Currently, there is no known role for continuation of aspirin in the postpartum period in at-risk patients and studies on the subject are limited.

While there are no definitive serum markers that can predict or diagnose preeclampsia, several have been studied as diagnostic tools. B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) are included. Resnik et al studied B-type natriuretic peptide (BNP) levels in 118 pregnant patients from first trimester to term gestation. In this study, patients with preeclampsia with severe features had significantly higher BNP levels than both patients with preeclampsia without severe features ($P<0.01$) or patients without hypertensive disorders of pregnancy (<0.01). They established a BNP cut-off of <40.6 as having a negative predictive value of 92% in excluding preeclampsia during pregnancy.[20] A 2013 systematic review supported this conclusion and found that patients with preeclampsia had significantly higher BNP in the third trimester, which was thought to be indicative of cardiovascular dysfunction associated with preeclampsia.[21] Additionally, BNP and NT-proBNP are currently widely used biomarkers for the diagnosis of heart failure and cardiovascular disease and risk-stratification for cardiovascular disease and long-term morbidity and mortality outside of pregnancy.[22-24]

Notably, however, there is no established "normal" BNP or NT-proBNP level during pregnancy or postpartum. Denoble et al compared NT-proBNP levels between obese and non-obese women throughout pregnancy at our institution and found that while NT-proBNP levels were lower in obese subjects during pregnancy, the difference was not significant in the postpartum setting.[25] In this study, the postpartum NT-proBNP in the obese population was 33 (27-56) and non-obese population was 23 (8-42).[25] Finally, Sheikh et al performed a meta-analysis of available literature on BNP and NT-proBNP levels during pregnancy and postpartum and found that both biomarkers are useful diagnostic tools for cardiac complications in both pregnant and recently delivered patients.[26]

There is currently no information on continuation of low-dose aspirin after delivery. However, the use of aspirin both during pregnancy in patients at risk for development of preeclampsia as well as for cardiovascular disease prophylaxis in high-risk patients outside of pregnancy suggests a possible protective benefit. With maternal morbidity and mortality increasing in the United States and cardiovascular disease being the number one cause, a better understanding of protective interventions against cardiac strain is paramount. This study hopes to evaluate the use of aspirin as a low-cost and accessible means to decrease long-term adverse maternal health outcomes. Evaluation of postpartum NT-proBNP levels in the postpartum period can help shed light on this important topic.

References:

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Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

This is a randomized-controlled trial of comparing NT-proBNP levels at 4-6 weeks postpartum between patients randomized to continuation of postpartum aspirin 81 mg for 6 weeks postpartum and placebo. Patients meeting inclusion criteria will be approached during routine prenatal visits, on arrival to Labor and Delivery, or following delivery for enrollment. Informed consent will be obtained, and patients will be randomized in a 1:1 fashion to aspirin 81 mg vs identical-appearing placebo to be continued for 6 weeks' postpartum. Patients will receive these medications prior to hospital discharge. Patients will be scheduled for routine postpartum follow-up appointment at 4-6 weeks as is standard of care at Duke. Patients will be reminded of their appointment via telephone call or text message the day prior to their scheduled follow-up visit. NT-proBNP levels will be drawn at the 4-6-week postpartum visit. This will b e one blood draw with a total of 10 mL collected. NT-proBNP levels will be compared between groups.

Patients will be eligible for randomization if they are 18 years of age or older, English-speaking, postpartum, have met USPSTF recommendations for low-dose aspirin use during pregnancy: $\geq$1 high risk factor (history of preeclampsia in prior pregnancy, multifetal gestational, chronic hypertension, preexisting diabetes, renal disease, autoimmune disease) or $\geq$2 moderate risk factors (nulliparity, obesity, family history of preeclampsia, sociodemographic characteristics, age 35 years or older, or personal history factors) and reported at least 50% compliance with aspirin during pregnancy. Patients will be excluded if they have had a hypersensitivity reaction to aspirin or other salicylates, history of gastrointestinal bleeding, history of gastric or duodenal ulcers, severe hepatic dysfunction, bleeding disorders and diathesis, known cardiac dysfunction with reduced ejection fraction, or are taking or prescribed ACE inhibitors. Patients requiring ICU admission during their pregnancy will be excluded.

Patients will be randomized in a 1:1 fashion to aspirin 81 mg vs identical-appearing placebo to be continued for 6 weeks' postpartum using a block randomization scheme implemented in RedCap.

The primary outcome for this analysis will be 4-6 week postpartum NT-proBNP levels. Secondary outcomes will be rates of preeclampsia diagnosis postpartum, rates of eclampsia, hospital readmission rates for blood pressure monitoring or cardiovascular disease work-up indications, number of subjects requiring initiation or increase in blood pressure medications, hospital readmission rates for bleeding-related complications, and rates of blood transfusions.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Patients will be eligible for randomization if they are 18 years of age and older, English-speaking, postpartum, have met USPSTF recommendations for low-dose aspirin use during pregnancy: $\geq$1 high risk factor (history of preeclampsia in prior pregnancy, multifetal gestational, chronic hypertension, preexisting diabetes, renal disease, autoimmune disease) or $\geq$2 moderate risk factors (nulliparity, obesity, family history of preeclampsia, sociodemographic characteristics, age 35 years or older, or personal history factors) and reported at least 50% compliance with aspirin during pregnancy.

Patients will be excluded if they have had a hypersensitivity reaction to aspirin or other salicylates, history of gastrointestinal bleeding, history of gastric or duodenal ulcers, severe hepatic dysfunction, bleeding disorders and diathesis, known cardiac dysfunction with reduced ejection fraction, or are taking or prescribed ACE inhibitors. Patients who required ICU level care during their pregnancy will be excluded.

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Patients will be approached for enrollment based on their eligibility in clinic, on admission to Labor and Delivery, or following delivery at Duke University. All patients who deliver at Duke University Hospital will be eligible for screening. Study staff will approach the subject and provide information regarding the study. If the patient is interested in participating, then study staff will obtain informed consent at that time.

The total goal enrollment is 114 participants (57 in each group). Patients will receive a $10 dollar gift certificate at their postpartum visit for participation in our study.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

We will not be including patients that do not have the capacity to give legally effective consent.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

The treatment group will be provided with a 6-week supply of 81 mg of aspirin prior to discharge from the delivery admission. The control group will receive a 6-week supply of placebo medication from the Investigational Pharmacy prior to discharge. The placebo will be identically appearing to the 81 mg aspirin. Patients will be scheduled for a 4-6 week postpartum clinic appointment, which is standard for these patients outside of this proposal.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant individuals, imprisoned persons or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

The use of low-dose aspirin during pregnancy has not been associated with a significantly increased risk of hemorrhage during the delivery course, and this dosage would not be expected to result in increased bleeding risk in the postpartum period.

While low-dose aspirin side effects are typically mild, patients may experience some, all, or none of the side effects listed below. Side effects will be assessed at the 4-6 week postpartum visit.

- Mild indigestion
- Nausea
- Vomiting
- Heartburn
- Increased bleeding tendency
- Nosebleeds
- Bleeding gums
- Stomach ulcers
- Wheezing
- Difficulty breathing
- Anaphylaxis

Given the overall minimal side effects associated with the use of low-dose aspirin as well as its routine use during pregnancy in a large subset of patients, identification of risk-mitigating interventions for long-term cardiovascular disease may improve long-term maternal health outcomes.

Low-dose aspirin is considered safe during breastfeeding. After aspirin ingestion, salicylic acid is excreted in breastmilk, with increasing levels detected with increased doses. With low doses of aspirin, defined as 75 to 325 mg daily, aspirin is not excreted in breast milk and salicylate levels are low. Therefore, low-dose aspirin is safe to administer in breastfeeding mothers.

There is also a small risk of loss of confidentiality and risk associated with a blood draw.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There is no anticipated cost to patients.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time

to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Baseline characteristics will be summarized by control and intervention group. Continuous variables will be summarized using mean (standard deviation) or median (25^{th} percentile, 75^{th} percentile) while categorical variables will be summarized using frequency (percentage). Primary outcome, NT-proBNP levels at 4-6 weeks postpartum, will be summarized and compared between groups using two-sample t-test or Wilcoxon rank sum test, depending on the empirical distribution of the data. Secondary outcomes will be compared between groups using the chi-square, Fisher's exact, Mann Whitney U, or student's t-tests, as appropriate. A p-value of M0.05 will be considered significant. Analyses will be performed in R 4.2.0 (R Core Team, 2022) or SAS 9.4 (SAS Institute Inc., Cary, NC).

A prior study at our institution found the following NT-proBNP levels in patients with and without obesity at 4-6 weeks postpartum:

NT-proBNP at 4-6 weeks postpartum	
Mean (SD)	37.4 (32.2)
Median	30.5
Q1, Q3	11.0, 47.0
Range	(2.5-135.0)

Using this mean and standard deviation with a target power of 0.8 at 0.05 level of significance, we calculated a sample size of 90 to detect a medium effect size (Cohen's d = 0.6), which is equivalent to a difference of 19.3 between control and intervention. To account for a 20% drop-out rate, we calculated a sample size of 114 (57 in each group).

This study is designed to be performed within a 24-month timeframe. Patient enrollment will start in spring 2023. Trained research staff will enroll patients in the clinic, on Labor and Delivery and postpartum with the goal to meet our sample size for enrollment by spring 2024.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

A Data Monitoring Committee (DMC) will be created to perform regular and timely review of data semi-annually in order to identify early, significant benefit or harm for patients while the trial is in progress. Non-identified safety data will be communicated to the DMC who will then meet to review the data. The DMC will be composed of three faculty members within the Duke University Department of Gynecology and Obstetrics. Individuals who are investigators or co-investigators cannot be members. Members must have no financial, scientific, or other conflicts of interest with the study. All investigators understand that the DMC serves as additional human subject's protection, but does not supplant reporting of significant adverse events to the Duke IRB. The DMC may devise its own stopping rules, and if there are significant numbers of adverse events, the DMC will recommend continuation, modification, or termination of the study after each meeting. This recommendation will be communicated to the Principle investigator who is responsible for reviewing the recommendation and forwarding it to the IRB. All investigators understand that the DMC may recommend their own "stopping rule" if other events occur which indicate a significant risk to study subjects.