Effectiveness of Higher Aspirin Dosing for Prevention of Preeclampsia in High Risk Obese Gravida: An open label, comparative effectiveness RCT (ASPREO Trial)

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Study Protocol

Principal Investigator: Farah Amro, M.D.

Co- Investigators: Conisha Holloman , M.D., Claudia Pedroza PhD , Baha Sibai, M.D.

Division of Maternal-Fetal Medicine

Department of Obstetrics, Gynecology and Reproductive Sciences

The University of Texas Health Science Center at Houston

UTHealth Houston
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1. BACKGROUND AND SIGNIFICANCE

Hypertensive diseases of pregnancy complicate around 10% of pregnancies. Preeclampsia is a pregnancy related hypertensive disorder. In the US during the past two decades the incidence of preeclampsia has increased by 25%. [1]The diagnosis of preeclampsia impacts the gestational age at delivery, with those with preeclampsia with severe features being delivered by 34 weeks gestational age, and those without being delivered by 37 weeks gestational age.[2] Preeclampsia is a major contributor to prematurity. Perinatal mortality is higher in infants of preeclamptic women regardless of gestational age at delivery. [3]Causes are hypothesized as placental insufficiency and placental abruption, which in turn cause either intrauterine fetal demise, or early delivery. Preeclampsia may also cause serious maternal adverse effects including: eclampsia (seizures), posterior reversible encephalopathy syndrome, placental abruption leading to disseminated intravascular coagulopathy amongst other maternal adverse outcomes. It is also associated with long term maternal health consequences, including long-term cardiovascular disease risk. [2]

Low dose aspirin was initially reported as having a beneficial effect at preeclampsia prevention in a case in 1978.[4] Since then there have been large randomized controlled trials with conflicting results regarding effectiveness of aspirin for preeclampsia prevention, and the optimal dosing. (table 1)

Table 1: Placebo based randomized trials of ASA ≤100mg for preeclampsia prophylaxis

Study Location Year	N	Gestational Age At Enrollment	Comparison	Preeclampsia Outcome
Wallenburg et al Netherlands 1986[5]	46	28 weeks	60mg ASA	Preeclampsia occurred in 30% (placebo) vs 0% (ASA), p<0.01.
McParland et al UK 1990[6]	148	24 weeks	75mg ASA	Preeclampsia occurred in 25% (placebo) vs 13% (ASA), not significant.

CLASP[7] **Multicenter 1994**	6927	12 -32 weeks	60 mg ASA	A nonsignificant reduction of 12% in rate of developing proteinuric pre-eclampsia.
ECPPA [8] **Brazil 1996**	1009	12 – 32 weeks	60 mg ASA	No significant difference in rate of preE in both groups.

Rationale for a clinical trial

Evidence suggests that in preeclamptic patients there is a imbalance in the prostacyclin /thromboxane balance favoring thromboxane. Thromboxane is a vasoconstrictor while prostacyclin is a vasodilator.[9] The pathophysiology of action of aspirin for preeclampsia prophylaxis is believed to be due to its preferential inhibition of COX-1 at low doses (60-150mg/day)[10].

The American College of Obstetrics and Gynecology in July 2018, published a committee opinion supporting the USPSTF guideline criteria for the use of low dose aspirin for preeclampsia prophylaxis. The recommended dose is 81mg/day of aspirin, and it is to be used in women at high risk for preeclampsia. Women were considered to be at high risk if they had at least a 8% incidence of preeclampsia (table 2). The initiation of aspirin was to be done at 12-28 weeks gestation, optimally prior to 16 weeks gestational age. [10]

Table 2: ACOG recommendations for low dose aspirin (LDA) use for preeclampsia prophylaxis

Risk Level	Risk Factors	Recommendations
High	History of preeclampsia	LDA if ≥ 1 Risk Factor
	Type 1 or 2 Diabetes	
	Chronic Hypertension	
	Multifetal Gestation	
	Renal Disease	

	Autoimmune Disease (SLE, APLS)	
Medium	BMI ≥ 30	LDA if > 1 Risk Factor
	Nulliparity	
	Fam. Hx of preE (mother or sister)	
	Sociodemographic characteristics (AAF, low SES)	
	Age ≥ 35	
	Personal Hx factors (hx of SGA , prior adverse pregnancy outcomes)	

As illustrated in table 3 there have been multiple randomized controlled trials that support the use of higher aspirin doses for preeclampsia prophylaxis. A recent systematic review and metaanalysis of randomized controlled trials, evaluating a total of 14,668 patients noted that the incidence of preeclampsia depended on the gestational age at initiation of aspirin and the dosing of aspirin used. With a clinically significant decrease in rate of preterm preeclampsia noted when the aspirin dose is ≥ 100 mg/day and when it is initiated at ≤ 16 weeks (table 4)[11].

Table 3: Randomized Trials with higher dose Aspirin for prevention of Preeclampsia

Study Location Year	Gestational Age at enrollment	N	Comparison	Preeclampsia Outcomes
Rolnik Multicenter Europe 2017[12]	11-14 weeks	1776	150mg ASA vs placebo	Preterm preeclampsia 4.3% in placebo group vs 1.6% in ASA

				group (p=0.0004)
Yu Multicenter International 2003[13]	22-24 weeks	844	150mg ASA vs placebo	19% in placebo group vs 19% in ASA group (p=0.6)
Sureau Multicenter France 1991[14]	15-18 weeks	229	150mg ASA vs 150mg ASA + dipyrimadole 225 mg/day vs placebo	No difference between groups.

Table 4: Metaanalysis with Relative Risk of preterm Preeclampsia detailed by onset of treatment and dose of aspirin

Dose	Trials Participants	Gestational Age	RR (95% CI)	P-value
< 100 mg	10 trials 11,855 pts	≤ 16 weeks	0.59 (0.29-1.19)	0.14
		> 16 weeks	1.00 (0.80-1.25)	0.99
≥ 100 mg	7 trials 2,813 pts	≤ 16 weeks	0.33 (0.19-0.57)	0.001
		> 16 weeks	0.88 (0.54-1.43)	0.60

Aspirin resistance is a phenomenon that refers to the inability of aspirin to reduce the production of thromboxane A2. It is detected by laboratory tests that either measure directly the thromboxane A2 levels, or indirectly the platelet function that depends on platelet thromboxane production.[15] A recent study evaluated aspirin resistance in pregnant patients, and noted that aspirin resistance was decreased as the dosing of aspirin increased. With a incidence of 30% , 10% and 5% of aspirin resistance at doses

of 81, 121 and 162mg respectively. [16] Moreover, data has emerged in other fields linking obesity, female gender, and poor glycemic control to aspirin resistance. [17]

At baseline, obesity is linked to a low grade inflammation state causing lipid peroxidation and in turn a persistent platelet activation, causing higher levels of thromboxane to be present in this population.[18] Also, obesity is a established risk factor for preeclampsia. [2]In a population-based cohort study including 503,179 nulliparous patients, obese patients had a fourfold increase in incidence of preeclampsia in comparison to those with a normal BMI.[19]

A metaanalysis published in the lancet in 2018 highlighted the effects of the interaction between bodyweight and aspirin dose in reducing vascular events.[20] This study concluded that patients with higher body weights need q higher aspirin dosage for secondary cardiovascular prevention. While other fields are also realizing the impact of bodyweight on aspirin effectiveness, we argue that this concept should be extended to our high risk obese patient population. A population which also inherently has a higher incidence of preeclampsia, higher baseline thromboxane levels, and may also have higher aspirin resistance. We thus propose that a “one dose fit all” approach may not be appropriate in this patient population. To our knowledge, at this time there are no randomized controlled trials that have compared aspirin 81mg and 162 mg in the pregnant obese patient population.

Hypothesis

We hypothesize that the administration of a higher dose of aspirin prophylaxis to a high risk obese population will result in a clinically significant decrease in rate of developing preeclampsia with severe features in comparison to the standard 81mg/day dose.

2. RESEARCH DESIGN AND METHODS

Objective
To compare the incidence of preeclampsia with severe features in the 81mg/day aspirin group to the 162mg/day aspirin group. Maternal and neonatal outcomes will also be compared between the two groups.

Population
Obese pregnant women with a singleton gestation at less than 20 weeks and either a history of preeclampsia in a prior pregnancy or stage I hypertension or pre-gestational diabetes.
Obese is defined as a BMI greater than 30 at time of the first prenatal visit.

Intervention
Aspirin at a dose of 162mg/day (ie two 81mg/day pills daily) to be started as early as 12 weeks gestational age till time of delivery

Control
Women who receive the standard recommended 81 mg/day dosing of aspirin from as early as 12 weeks gestational age till time of delivery

Outcome (Primary)

Incidence of preeclampsia

Preeclampsia with severe features diagnosis will be abstracted from the medical charts. This will be used for the primary outcome. The diagnosis will then be adjudicated by three maternal fetal medicine specialists, to assess for compliance with ACOG established criteria.[2] The adjudicated diagnosis will be used for the measurement of the secondary outcome.

Other Secondary Outcomes

- Maternal Outcomes
  - Incidence of preterm preeclampsia
  - Gestational Hypertension
  - Abruption
  - Eclampsia
  - HELLP syndrome
  - Postpartum Hemorrhage
  - Other maternal bleeding (?)
  - Need for blood transfusion
- Neonatal Outcomes
  - Gestational age at delivery
  - Delivery at < 37 weeks
  - Apgar score at 5 min ≤ 5
  - Small for gestational age
  - NICU length of stay
  - Intraventricular Hemorrhage Grade III-IV
  - Bronchopulmonary Dysplasia
  - Necrotizing Enterocolitis

Study Design

Randomized controlled open-label comparative effectiveness trial.

Inclusion Criteria

- A singleton gestation at less than 20 weeks at time of enrollment, with a BMI greater than or equal to 30 and one of the following:

1. **History of preeclampsia in a prior pregnancy**
   -Diagnosis will be obtained by review of records, and if unavailable then patient history. Preeclampsia diagnosis may be made in antepartum or postpartum period.

   OR

2. At least **stage I hypertension during pregnancy**
   -Stage I hypertension is defined as a systolic blood pressure between 130-139 mm Hg or diastolic blood pressure between 80-89 mm Hg[21]

-This blood pressure criteria is met regardless of medication usage

- The patient must have a blood pressure reading ≥ 130-139/80-89 mm Hg at least during 1 clinic visit during the current pregnancy; before or at time of enrollment

OR

3. **Pre-gestational diabetes**
   -Type 1 and Type 2 diabetics are included
   -Gestational diabetes mellitus diagnosed prior to 20 weeks gestational age will also be included

Exclusion Criteria

- ***Known allergy/prior adverse reaction/any medical condition where aspirin is contraindicated***
- ***Already on aspirin prior to pregnancy***
- ***Baseline renal Disease***
- ***Baseline Proteinurea identified at time of enrollment, defined as urine analysis with 3+ protein, or urine protein to creatinine ratio ≥0.3***
- ***Seizure disorder on medications***
- ***Known major fetal anomalies***
- ***Multifetal gestation***

Recruitment

Patients will be recruited from the following locations:

- Texas Medical center Ross Clinic in the UT Professional Building (Suite 350)
- Texas Medical center High Risk OB Clinic in the UT Professional Building (Suite 350)
- UT Obstetrics office at Bellaire
- Harris Health Obstetrics Clinic at LBJ Hospital

Randomization

Randomization will be achieved by computer-generated random sequences, using RedCap. Permuted block randomization will be performed. Women will be randomized to 81mg/day of aspirin or 162 mg/day of aspirin.

Interventions and Procedures

Women with singleton gestations that are less than twenty weeks gestational age and meet inclusion criteria will be approached by the research staff after the study is introduced by the patient's provider. Written informed consent will be obtained from participating women at the outpatient clinic. If the patient consents, then randomization

will be performed. The results of randomization will be shared with the obstetric provider and the patient prior to starting aspirin. If the patient had already been started on

81mg/day aspirin in a prior visit then she will be informed of whether she should continue with the same dose or if she would need a higher dose based on the randomization.

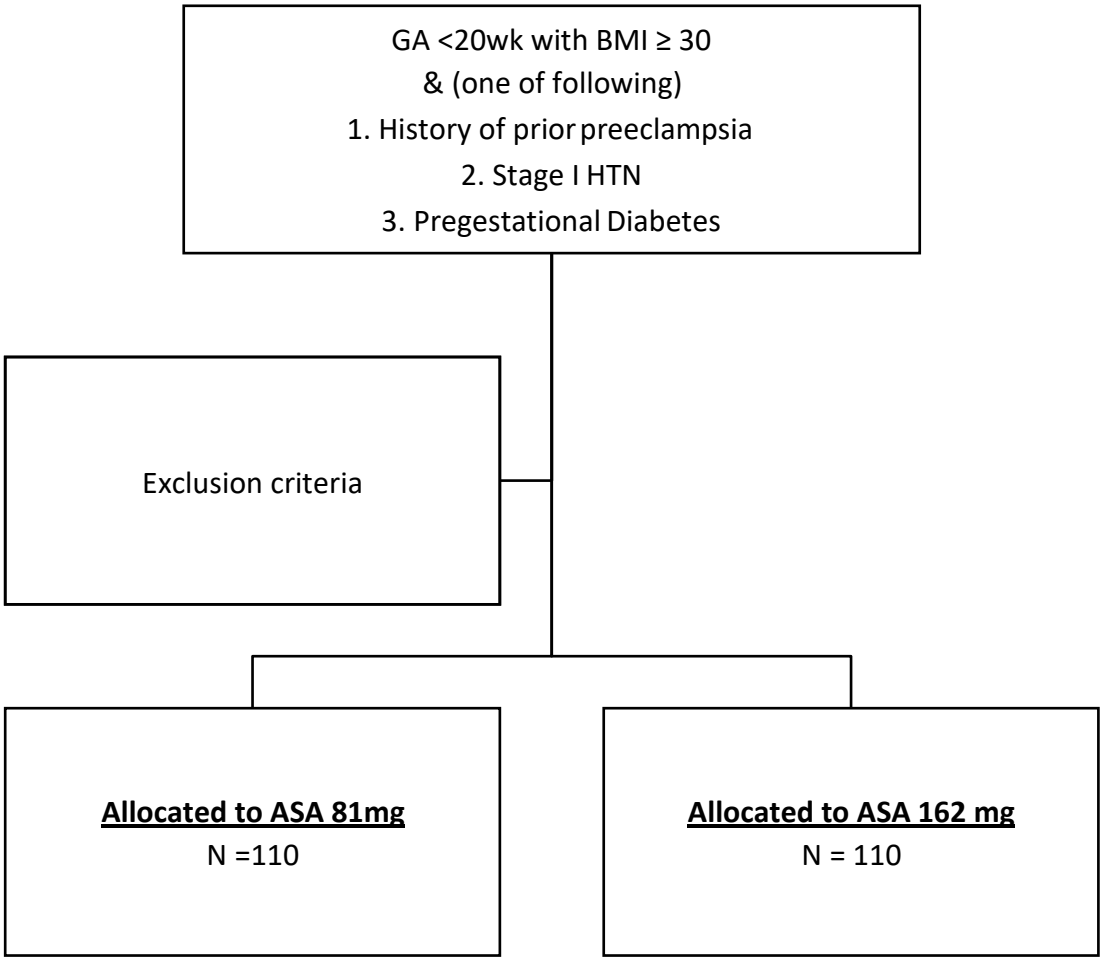
After randomization, patients will then be prescribed the medication. Which will be started between 12 and 20 weeks gestational age and continued till time of delivery. The primary provider will dictate all other aspects of care.

A medication adherence survey (Morisky medication adherence survey) will be performed to assess for compliance at 16-24 weeks of gestational age, and again at 32- 36 weeks gestational age. At the time of administration of medication adherence surveys, participants will be asked about medication side effects. [22-24]

Blood samples (3-4 cc) and urine samples (3-4 cc) will be obtained at the time of enrollment (with the routine blood tests that are sent), to test for baseline aspirin, thromboxane and prostacyclin levels. At the time of delivery, blood samples (3-4 cc) and urine samples (3-4 cc) (with routine blood samples that are sent at time of labor admission), placental 1x1 cm specimens and cord blood will be obtained. These samples will be used for biochemical correlation with the clinical data.

The primary outcome (incidence of preeclampsia with severe features) will be determined based on clinician diagnosis, with the use of ACOG diagnostic criteria. Secondary outcomes will be determined by following the mother and the neonate clinically until the time of discharge. Patients will not be contacted after discharge from the hospital.

Figure 1. Flow Diagram



Sample Size and Feasibility

An intent-to-treat principle will be applied to all analysis. To calculate Bayesian statistical power we assumed a baseline incidence of preeclampsia in our population to be 20%. We investigated effects sizes of 50%, 40%, and 30% reduction (corresponding relative risk [RR] of 0.5, 0.6, and 0.7). We also varied the level of certainty (probability threshold for declaring benefit) from 70% to 85%. For all scenarios, we assumed a neutral prior centered at RR of 1.0 with 95% credible interval of 0.33-3.0 (excludes implausible large treatment effects). Tables 5 and 6 present the power for two total sample sizes. We will use the number of patients required to detect a 40% reduction in incidence of preeclampsia with 75% certainty and power $(1 - \beta) = 0.80$ is **220** (110 patients in each arm).

Table 5: Bayesian power for sample size **N=290** using different levels of certainty				
	Level of Certainty			
Assumed RR	70%	75%	80%	85%
0.50	0.97	0.95	0.93	0.89
0.60	0.91	0.88	0.83	0.76
0.70	**0.80**	0.75	0.68	0.59

Table 6: Bayesian power for sample size **N=220** using different levels of certainty				
	Level of Certainty			
Assumed RR	70%	75%	80%	85%
0.50	0.93	0.9	0.86	0.81
0.60	0.84	**0.80**	0.74	0.67
0.70	0.71	0.66	0.59	0.5

In the week of November 5-9 2018, 10 patients that attended the UT Women's clinic and UT Bellaire Clinic, met inclusion criteria. Assuming a 50% enrollment rate, the study would take 12.5 months.

Statistical Tests

Selected baseline characteristics and outcome measures will be collected for each group. Descriptive statistics will be used to summarize all variables. An intent-to-treat analysis will be conducted. The rate of the primary outcome, preeclampsia, will be compared between the intervention and control group using a log binomial (or Poisson in case of nonconvergence) model to estimate relative risk and 95% confidence interval (CI). Each secondary outcome will be similarly analyzed using the best fitting generalized linear model with intervention group as the covariate. For all outcomes, we will report relative risks or differences and 95% CIs.

We will also conduct a Bayesian analysis of the primary outcome to calculate probability of treatment benefit or harm. We will use a neutral prior distribution for the intervention effect that excludes implausible large treatment effects: Normal(0, SD=0.57) in the log RR scale (prior 95% interval for the RR of 0.33-3) [25]. We will report posterior median and 95% credible interval and probability of treatment benefit.

Subgroup Analysis. To investigate treatment effect modifier for the primary outcome, we will use a Bayesian hierarchical model with terms of interaction between treatment group (162 mg, 81 mg) and the prespecified potential moderator of BMI (30-40; >40). The conservative Bayesian approach of Dixon and Simon [26] allows us to specify a priori how likely (or unlikely) it is for subgroup differences to be present and to shrinkthe subgroup estimates to the overall mean treatment effect. A neutral prior will be used for the interaction term. Point estimates of treatment effect and 95% credible intervals will be reported along with probability of treatment benefit/harm.

3. SAFETY ASSESSMENT

A. Maternal Risk

According to a USPSTF report discussing low-dose aspirin use for the prevention of preeclampsia, there was no increased risk of placental abruption (RR: 1.17; CI, 0.93-1.48) in 11 trials (23,332 women). No increased risk of postpartum hemorrhage (RR: 1.02; CI 0.96-1.09) in 9 trials (22,760 women) and no difference in mean blood loss (5 trials; 2,478 women). [27]

In the EPREDA trial (150mg ASA administered) they noted no abnormal bleeding in mothers nor babies. [28] In the multicenter RCT done by Yu et al, with administration of 150 mg ASA in comparison to placebo, no statistically significant differences in the rates of placental abruption (4% vs 2%, p=0.12), postpartum hemorrhage (25% vs 26%, p=0.67) and blood transfusions (2.5 vs 2.2%, p=0.81) were observed between the groups.

B. Fetal Risk

A review of 11 trials (which included 23,332 participants), noted no significant harm of perinatal death or abruption to those receiving aspirin in comparison to those that did not. Of the 10 trials reporting on neonatal intracranial hemorrhage, the fixed-affects pooled risk ratio was 0.84 (CI, 0.61 to 1.16). [29] In a cohort of 15,000 women that reported aspirin use in the first trimester, there was no increased risk of congenital malformations. [30] Furthermore, the use of low dose aspirin in the third trimester, has not been found to be associated with early ductal closure. [31] A 2007 cochrane meta-analysis which reviewed 10 trials (including 26, 148 infants) did not find an increased risk of neonatal intracranial hemorrhage, in relation to the use of low dose aspirin in the third trimester.[32]

Management of Adverse Events

Any adverse events will be reported to the Committee for the Protection of Human Subjects (CPHS). Because this study involves the use of aspirin at low doses there is no increased anticipation of severe adverse events.

Procedures in the Event of Abnormal Clinical Findings

In the event of an abnormal clinical finding, the health care provider caring for the participant will be notified to allow treatment in the usual clinical manner.

Institutional Review Board

Before initiation of the study, the PI will obtain approval of the research protocol from the IRB. The study will be registered in www.clinicaltrials.gov as required by US law for public access.

Specification of Safety Parameters

The proposed trial is intended to evaluate the impact of different low doses of aspirin on rates of preeclampsia. Aspirin at the desired doses have been used safely during pregnancy.

The PI, who will also determine the safety parameters, will carefully monitor patient safety. The PI or designee will notify the IRB of applicable events according to institutional guidelines.

4. ETHICAL CONSIDERATIONS

Informed Consent

The study will be introduced to potentialsubjects from their care providers. Research staff will be present to answer any questions about the study. Both verbal and written subject consent will be obtained prior to the commencement of any study procedures. Consent will be obtained by a person fluent in their language, English or Spanish. A patient research authorization form (as required by the HIPAA Privacy Rule) will also be obtained in the same manner. A copy of the signed consent form and patient research authorization form will be provided to the patient and placed in the hospital EMR.

All prospective study candidates will be given a full explanation of the consent form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the Investigator is assured that the individual understands the requirements of the study, the subject will be asked to sign the consent. The Investigator shall provide a copy of the signed and dated informed consent to the patient and the original shall be maintained in the patient's study files. Patients who do not sign the consent form will not be permitted to participate in the study.

Data Collection

For this protocol, web data entry screens corresponding to the data collection forms will be entered electronically in the REDCap Database.

Institutional Review Board

Before initiation of the study, the PI will obtain approval of the research protocol and from the IRB. The study will be registered in www.clinicaltrials.gov as required by the US law for publicaccess.

Subject Confidentiality

A linking log will be created that will link patients with a patient number. Strict confidentiality of their patient data may be reviewed for study purposes by authorized individuals other than their treating physician. Patient, neonatal and delivery information will be recorded on datasheets that

will be stored in a locked file cabinet in the PI's office, which is also locked. Information will be entered into a secured REDCap database that is password protected and maintained on a UT computer, which are password protected.

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