The Effect of Ibuprofen on Post-partum Blood Pressure in Women With Hypertensive Disorders of Pregnancy

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OBGYN Research Program Study Protocol Template

Title: A randomized-controlled trial to assess the effect of ibuprofen on post-partum blood pressure in women with hypertensive disorders of pregnancy

Principal Investigator: Elizabeth Langen, MD

Co-Investigators: Alexander Tsodikov, PhD; Jourdan Triebwasser, MD, MA

1. Objective

To assess the effect of routine doses of ibuprofen on post-partum blood pressure control in women with gestational hypertension (gHTN) or preeclampsia without severe features (preE).

2. Specific Aims

Hypothesis: When compared to acetaminophen, ibuprofen does not increase post-partum systolic blood pressure (SBP) above baseline to a clinically relevant degree (≥10 mmHg) in women with gHTN and preE.

Aim 1: To assess the mean difference in SBP during 24 hours of exposure to ibuprofen and acetaminophen.

Aim 2: To assess whether ibuprofen results in higher satisfaction with pain control in the immediate post-partum period (48 hours) compared to acetaminophen.

Aim 3: To prospectively assess the need for post-partum anti-hypertensive therapy and readmission for blood pressure control in women with gHTN and preE. The post-partum period is defined as delivery through 6 weeks after delivery.

3. Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for post-partum analgesia. This use is supported by limited data on post-partum pain specifically; however, ibuprofen and other NSAIDs are superior to acetaminophen in ameliorating uterine pain and cramping in dysmenorrhea.[1-4] The effect of NSAIDs on blood pressure (BP) in women post-partum is less well-known. In non-pregnant hypertensive patients NSAIDs are associated with increased BP over short courses of days to months, though effects of various NSAIDs differ.[5,6] Pooled analyses suggest changes in mean BP of up to 3-6 mm Hg depending on the measurement method.[5,6] There are case reports of hypertensive crises after NSAID administration post-partum in both normotensive and hypertensive women.[7] A larger, recent retrospective cohort study found no difference in mean arterial pressure (MAP) or need for antihypertensive therapy in women with severe hypertensive disorders of pregnancy who were exposed to NSAIDs post-partum.[8]

In light of the potential for worsening blood pressure in women with hypertensive disorders of pregnancy, the Task Force on Hypertension in Pregnancy of American College of Obstetricians and Gynecologists stated that “providers should be reminded of the contribution of nonsteroidal anti-inflammatory agents to increased BP.” Additionally the task force recommends that NSAIDS “be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum”.[9] However, provider practices since the publication of these guidelines have varied.

4. Study Team Expertise

Elizabeth Langen, MD, is an Assistant Professor in the Department of Obstetrics and Gynecology in the Division of Maternal Fetal Medicine. She is director of research for the division of Maternal-Fetal Medicine. Her research has focused on both the causes and prevention of preterm birth, as well as evaluation of normal labor and has included both prospective observational and randomized controlled trials.

Jourdan Triebwasser, MD, MA, is a fellow in the Department of Obstetrics and Gynecology in the Division of Maternal Fetal Medicine. She has training in study design, biostatistics, and scientific writing through Master's-level coursework. She has previously recruited participants to randomized-controlled trials involving obstetric patients.

Alexander Tsodikov, PhD: Professor of Biostatistics. Alexander is a faculty member of the Michigan Institute for Clinical & Health Research (MICHR) Biostatistics Group. Dr. Tsodikov's research interests are in various areas of biostatistics and biomathematics, including failure time and survival analysis models, cure models, semiparametric inference, stochastic models, optimal control, and inference algorithms based on self-consistency.

Marjorie C. Treadwell, MD, is a Professor of Obstetrics and Gynecology with specialty certification in Maternal Fetal Medicine. With a primary interest in prenatal diagnosis and fetal therapy, she has worked closely with sub-specialists across the spectrum of pediatrics and adult medicine to advance the knowledge as well as clinical care of fetal conditions. While at Wayne State University, she worked closely with the extramural Perinatal Research Branch of the NIH. Multiple publications resulted from the collaborative relationship with that group, predominantly in the area of improving diagnosis and understanding of fetal cardiac abnormalities. Since being based at the University of Michigan, she represents our fetal therapy program in the North American Fetal Therapy Network (NAFTNet), which is a consortium of (currently) 24 fetal therapy centers across North America. University of Michigan participates in several multicenter trials and projects through this organization. Within the university, we recently completed a project with Radiology utilizing software developed by our biomedical team developing an innovative method of determining volume flow in patients with high risk pregnancies. As the Director, Fetal Diagnostic Center, she facilitates and coordinates multiple projects recruiting from our prenatal unit. These projects involve multiple specialties across the spectrum of medicine and basic science.

Lori J. Day, MD, is a Clinical Assistant Professor of Maternal Fetal Medicine. Her research interests include genetic contribution to prematurity and the physiology of premature labor. She has engaged in research specimen collection and storage for women in term and preterm labor and their newborns.

Deborah Berman, MD, is an Associate Professor of Maternal Fetal Medicine. Her research interests include prenatal diagnosis, counseling, and management of fetal anomalies. Additionally, she has been a long time member and participant in the Perinatal Mood Disorders Team, collaborating on research on women with mood disorders throughout the pre-pregnancy, prenatal, and postpartum periods. She is actively involved in research on impaired fetal growth and other deleterious effects of

depression in pregnant women, as well as maternal and fetal outcomes at a clinical and biochemical level in pregnancies complicated by maternal mood disorders. She is collaborating on a project with the School of Social Work that focuses on the mental health of male partners throughout pregnancy. Additionally, she had multidisciplinary collaborations on the neuroprotective effects and biochemical changes with Docosohexanoic Acid administration in models of intrapartum hypoxia-ischemia (HI) and neonatal encephalopathy.

Clark Nugent, MD, is a Clinical Professor of Maternal Fetal Medicine. His prior research has included work on ultrasound assessment of the cervix and multiple gestation.

Cosmas JM Van de Ven, MD, is the J. Robert Willson Professor of Obstetrics and the Director of Maternal Fetal Medicine in the Department of OBGYN. In the early 1980's Dr. Van de Ven studied the role of sodium and potassium channels in the setting of hypertension in the department of physiology at UofM. This interest transitioned to endothelial cell function and paracrine control of the vascular smooth muscle in the setting of pre-eclampsia. Dr. Van de Ven's clinical interest focusses on maternal physiology and pathology. He is engaged in many departmental and institutional committees and administrative functions.

Alissa Carver, MD, is a Clinical Assistant Professor of Maternal Fetal Medicine. Her prior research has included work on preeclampsia, multifetal gestation, maternal infection, and labor.

Mark Chames, MD, is a Clinical Assistant Professor in the Department of Obstetrics and Gynecology and specializes in Maternal and Fetal medicine with clinical interests in ultrasound, multiple pregnancies and medical complications and pregnancy with focus on hypersensitive disorders and diabetes.

5. Methodology

i. *Trial design:*

1. Cross-over randomized trial with 1:1 allocation ratio.
2. Double-blind design with drug encapsulation performed by research pharmacy.
3. Intervention (ibuprofen), control (acetaminophen).

ii. *Inclusion/Exclusion Criteria*

Inclusion:

1. Antepartum women diagnosed with gHTN or preE by blood pressure ≥140 systolic or ≥90 diastolic, on at least 2 measurements ≥ 4 hours apart; with or without proteinuria (urine protein-creatinine ratio ≥0.3 or 24 hour-urine protein ≥300 mg).
2. 18-45 years of age.
3. Taking one or fewer oral medications for blood pressure control.
4. Singleton gestation.
5. English-speaking.

Exclusion:

i. Allergy to NSAIDs, aspirin, or acetaminophen.
ii. Severe features of preeclampsia prior to enrollment:

a. More than 1 severe range blood pressure (≥160 systolic or ≥110 diastolic).
b. Neurologic symptoms attributed to hypertension (headache, visual changes).
c. Pulmonary edema.
d. Elevated AST (>60 international units/L) or ALT (>70 international units/L).
e. Low platelet count (<100,000/microliter).
f. Renal insufficiency (creatinine > 1.1 or double the baseline creatinine if known).

iii. Chronic hypertension defined as hypertension pre-existing pregnancy or diagnosed prior to 20-weeks' gestation.
iv. Moderate- or severe-persistent asthma.
v. Therapeutic anticoagulation.
vi. Chronic opiate use during the pregnancy (opiate therapy given daily for > 2 weeks).
vii. Lactose intolerance or allergy due to placebo containing lactose.
viii. Cesarean delivery.
ix. Additional anesthesia at time of delivery (spinal anesthesia, sedation) that would change routine pain management.

iii. *Recruitment Plan and Study Design*

1. Number of Subjects: 40 (see details of power calculation in statistical analysis plan); however, we anticipate that up to 300 women will sign consent to participate in the trial in order to have 40 women undergo randomization.
2. Method of Contact and Consenting:

1. Antepartum Recruitment:
    a. Patients with diagnoses of gHTN and preE will be recruited as outpatients through the Fetal Diagnostic Center and OB-Gyn clinics at VonVoightlander Women's Hospital. Study team members will review daily appointments in MiChart to determine eligibility.
    b. Once the patient is determine eligible a study team member will approach the potential subject prior to or after their scheduled appointment.
2. Intrapartum Recruitment:
    a. Patients admitted to Labor & Delivery at VonVoightlander Women's Hospital with diagnoses of gHTN and preE will also be recruited if not previously approached as an outpatient. Study team members will identify potential participants through monitoring triage admissions through the electronic medical system.
    b. To reduce possible burden on the participants who have personal or medical situations that might make recruitment contact upon check-in to triage distressing, we have added a step of contacting the attending provider or nurse prior to approaching the women. This will decrease the likelihood of recruiting someone

where special factors, such as a difficult social situation, exist.

c. Once we consult with the provider to make sure they feel it would be acceptable for us to contact the potential volunteer, a study team member will approach the woman and explain the study. The potential participant will then be approached in a private location (such as a patient room) to discuss possible enrollment. If enrollment is declined, a record will be made that the study was offered and declined so that the study team does not approach the participant again.

3. Written informed consent will be obtained if all inclusion/exclusion criteria are satisfied at time of recruitment.
4. If exclusion criteria develop in the interim (i.e. thrombocytopenia) between recruitment and delivery, the participant will not be randomized. However, data from their delivery admission and post-partum period will be collected to compare to women who maintained trial eligibility.

3. Method of Interaction/Procedure/Intervention:
   1. At the time the participant signs the consent document, a study team member will administer a survey to capture demographic and obstetric characteristics of participants.
   2. Patients will be managed intrapartum without regard to study involvement. Mode of delivery will be determined by routine obstetric indications.
   3. If a participant undergoes cesarean delivery, she will not be randomized.
   4. At the time of delivery, eligibility will be reviewed. If the participant remains eligible, she will be randomized by the study pharmacy to begin post-partum analgesic therapy with ibuprofen or acetaminophen. Providers will be blinded to allocation group.
   5. The intervention will be conducted in cross over-fashion. Either ibuprofen or acetaminophen will be given for 24 hours with time starting at first dispense time (period 1). Then the other drug will be given for the subsequent 24 hours (period 2).
      a. Study drugs will be encapsulated for blinding purposes and given with in the following schedule: ibuprofen (600 mg every 6 hours) or acetaminophen (650 mg every 6 hours).
      b. The study drug doses will come in packets. Ibuprofen packets will have three 200 mg tabs. Acetaminophen packets will have two 325 mg tabs and one placebo tab.
      c. Oxycodone will be available for uncontrolled pain (5-10 mg every 6 hours as needed). The number of doses taken will be recorded as measure of pain control.
   6. Pain assessment:

a. Prior to the first dose of pain medication, participants will take a brief, self-administered survey to assess pain.
    i. Abdominal pain and perineal pain will be assessed separately using 0 (no pain) to 10 (worst possible pain) scale.
    ii. Overall pain will also be assessed using 0 (no pain) to 10 (worst possible pain) scale.
b. Two hours after the first dose of study drug, participants will repeat the self-administered survey to assess abdominal, perineal, and overall pain using a 0-10 scale.
c. Pain scores as assessed by nursing will also be abstracted from the medical record.
d. A brief survey on satisfaction with pain control during period 1 and period 2, as well as overall during post-partum stay will be administered prior to discharge.
    i. Satisfaction will be assessed using a 5-point scale of (1) not at all satisfied (2) slightly satisfied (3) moderately satisfied (4) very satisfied (5) extremely satisfied.

7. Blood pressure assessment:
    a. Standard blood pressure monitoring per post-partum protocol: every 15 min x 1 hour, then every 30 min x 1 hour, then every 4-8 hours until discharge per the discretion of the treating team.
        i. Additional blood pressures may be recorded according to provider preference (i.e. concern for spurious value, need to initiate antihypertensive therapy).
    b. Additional blood pressure monitoring will be performed during the period of study drug administration using a Spacelabs model 90207 ambulatory blood pressure monitor beginning at the time of first pain medication administration. This monitor has been validated in pregnant patients.[10]
        i. The monitor will be set to record values every 60 minutes.
        ii. The blood pressure monitor display will be covered in the accompanying carrying pouch to blind participants and providers to values.
        iii. The ambulatory blood pressure monitor will be discontinued after period 2 is complete.
8. If the participant remains inpatient beyond the 48 hours of study drug administration, she will be given pain medication according to provider preference.
9. Initiating antihypertensive therapy, repeating lab tests (creatinine, liver function tests, blood counts), time of discharge, and discharge pain medications will be at the discretion of treating physicians.

a. Antihypertensives are generally initiated with sustained SBP >150 mmHG at our institution.
b. Discharge prescriptions for pain medications will be recorded.

10. Data will be abstracted from the medical record regarding delivery, anesthesia, medical comorbidities, post-partum blood pressures readings, antihypertensives given, need for magnesium, pain medication usage, and hospital readmission.

Study Schedule
Recruitment • Outpatient with diagnosis of preE or gHTN. • Inpatient-if not previously approached as an outpatient or with new diagnosis of preE or gHTN upon admission.
Consent • Written informed consent will be obtained if all inclusion/exclusion criteria are satisfied at time of recruitment.
Randomization • Eligibility criteria reviewed at time of delivery. • If participant remains eligible, will be randomized to ibuprofen/acetaminophen versus acetaminophen/ibuprofen by research pharmacy.
Intervention • Pain medications will be dispensed by the research pharmacy and administered by floor nurses. • Blood pressure monitoring o Standard post-partum blood pressure monitoring will be performed by floor nurses and abstracted from the medical record. o Ambulatory blood pressure monitoring (Spacelabs model 90207) will be performed during 48 hours of study drug administration. • Inpatient pain assessment o Pain survey will be administered prior to first dose of medication in period 1. o Pain survey will be repeated 2 hours after first dose of medication in period 1. o Pain control satisfaction survey administered prior to discharge.
Data abstraction • The following will be abstracted from the electronic medical record after hospital discharge until 6 weeks post-partum: delivery mode, anesthesia, medical comorbidities, post-partum blood pressures readings, antihypertensives given, need for magnesium, pain medication usage, and hospital readmission.

Compensation: $25 check per participant who undergoes randomization. This is a one-time payment for participation.

iv. *Subject Withdrawal*

1. Under what conditions will a subject be withdrawn prior to completion:
    1. Those who develop any exclusion criteria between enrollment and delivery.
    2. Those who require a second increase in antihypertensive medications post-partum.
    3. Those who develop renal insufficiency (creatinine > 1.1 or double the baseline creatinine).
    4. Those who develop thrombocytopenia (platelets < 100,000/μL).
2. If a subject withdraws prior to completion, what is the plan for the use of their data:
    1. If the participant withdraws prior to randomization, data on baseline characteristics, hospital course, and post-partum course will continue to be collected and analyzed unless the participant requests otherwise in writing.
    2. If the participant underwent randomization, data on hospital course and post-partum course will continue to be collected and analyzed. Her information will be included in intention-to-treat analysis.

v. *Data Retention and/or Data Destruction Plan:*

The patient data will be entered from paper enrollment forms into a REDCap database. All PHI will be marked as such in the REDCap database. When data is downloaded for analysis, no PHI will be downloaded from the REDCap database. REDCap is a secure web application designed to support data capture for research studies. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Physical security for the databases is provided in a professionally managed and equipped tier-2data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos/Level 1 and UMHS Level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure are consistent with industry best practices including HIPAA security and privacy requirements and the HITECH Act. The application provides audit trails on user access to MICHR and MSIS technical and support teams. Data will subsequently be deleted after being maintained for the prescribed period of time post study closure. The original signed consent forms will be kept in a locked office in the University of Michigan Hospital. These will be destroyed in hospital PHI destruction bins after being maintained for the prescribed period of time post study closure.

6. Risks & Benefits

i. Risks:

1. Possible increase in blood pressure with ibuprofen (Rare)
2. Risks of ibuprofen (package labeling warnings)
    a. Severe allergic reaction, especially in people allergic to aspirin (Rare)
        i. Hives
        ii. Facial swelling
        iii. Asthma/wheezing
        iv. Shock

v. Skin reddening
vi. Rash
vii. Blisters

b. Severe stomach bleeding (Rare)
i. Risk is higher if you are age 60 or older, have had a stomach ulcer or bleeding, take a blood thinning (anticoagulant) or steroid drug, take other drugs containing prescription or non-prescription NSAIDs, have 3 or more alcoholic drinks every day while using this product

c. The risk of heart attack or stroke may increase if you use more than directed or for longer than directed. (Rare)

3. Risks of acetaminophen (package labeling warnings)
a. Severe liver damage (Rare)
i. Risk is higher if you take more than 4 grams in 24 hours, with other drugs containing acetaminophen, or with 3 or more alcoholic drinks every day while using this product.

ii. Benefits:
1. Likely better pain control when receiving ibuprofen.

7. **Study Agent**

The study agents (ibuprofen and acetaminophen) will be procured by Research Pharmacy (RP) from commercial supply; RP will compound into blinded supply by over-encapsulating the tablets in matching gelatin capsules. RP will package the blinded supplies into kits as follows: the ibuprofen packets will have three 200 mg tablets and acetaminophen packets will have two 325 mg tablets and 1 placebo tablet. The placebo tablet will contain lactose. The Research Pharmacy will be responsible for drug accountability according to their standard SOPs for drug accountability. The medications will be administered by floor nurses.

8. Statistical Design

Randomization:

- A random allocation sequence using 1:1 allocation will be generated by the biostatistician and provided to the research pharmacy.
- Allocation concealment mechanism: randomization sequence given directly to study pharmacy. Providers will call study pharmacy at time of delivery with randomization number. This will be unblinded at the completion of study recruitment.

Blinding:

- Providers and participants blind to treatment allocation with capsules from pharmacy.

Statistical methods:

Sample size calculation:

- There is limited post-partum or short-term NSAID data from which to base our sample size.

- In a study of hypertensive men and women treated with NSAIDs or placebo for 4 weeks, the standard deviation of the difference in BP from baseline of 13 mmHg was observed.[11]
- We are assuming the margin of equivalence (equivalence limit difference) to be approximately 10 mmHg. We also assume that intra-participant variation will be less than across-group variation seen in the Palmer study; we then assume a standard deviation of 8 mmHg.
- With these parameters, a two-sided test of equivalence performed at the significance level of 0.05 will have at least 80% power to prove the hypothesis of equivalence with a total of 44 measurements. We are planning to recruit 40 women over 12 months. This will bring the expected number of measurements available for the analysis (accounting for each woman bringing two-measurement in a cross-over trial) to 68 with a 15% expected drop-out rate. The reserve of sample size will be used to ensure we have more power to detect the carry-over effects of treatment into the next study drug period.

Primary outcome: difference in SBP from baseline during 24 hours of drug exposure.

- Baseline SBP will be calculated as the arithmetic mean of the initial 5 blood pressures recorded after admission for labor or induction of labor.
- A linear mixed model with Gaussian subject-specific intercept term will be used to regress the longitudinal BP measurements on the treatment type, group (Ibuprofen-Acetaminophen, Acetaminophen-Ibuprofen), and time. The main effect of time that expresses differences at baseline before the drugs had a chance to have an effect will likely be removed from the model as no such differences are expected due to randomization. The time by treatment and group interaction terms will be of main interest. The primary hypothesis is that of equivalence. Equivalence testing (no meaningful difference in BP between the two drugs) will be done using two one-sided 95% confidence intervals for the regression parameter representing the effect. The hypothesis of equivalence will be accepted if the intersection of the two one-sided intervals is contained entirely inside the region of equivalence.

Secondary outcomes:

- Mean change in pain score after 1 dose of pain medication
- Satisfaction with pain control (treated as an ordinal categorical score)
    - Linear models will be used to analyze pain. Ordinal logistic regression (the Proportional Odds Model) will be used to analyze the satisfaction endpoint. Hypotheses of significance will be tested by the likelihood ratio test. Model diagnostics will be performed using standardized residual plots. Variable transformations and Generalized Linear (Mixed) Models will be considered with continuous responses in case model diagnostics reveals a departure from linearity or normality assumptions. Reasons for missing data will be analyzed using a multinomial logistic model. Analysis results with missing data excluded will be presented along with the analysis where missing data will be imputed using predictive matching.

- Need for antihypertensive therapy in the post-partum period (descriptive statistics only)
- Incidence of severe hypertension during period 1 versus period 2 (Fisher exact test) and during the post-partum period (descriptive statistics only).

Descriptive statistics such as means and proportions will be calculated for each variable of interest (obstetric and demographic characteristics). Statistically significant differences will be assessed at the $p<.05$ level. Data will be analyzed using R and SAS 9.4 (SAS Institute, Cary, NC).

9. Adverse Event Reporting

Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigation study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a) *Definitely related:* clearly associated with study drug/treatment
b) *Probably related:* likely associated with study drug/treatment
c) *Possibly related:* may be associated with study drug or other treatment
d) *Unlikely to be related* or
e) *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of the following criteria are met:

a) There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b) There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c) The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d) A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a) Death
b) A life-threatening adverse drug experience
c) A persistent or significant disability and/or incapacity
d) A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may required medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.

Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may required medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the package inserts or in the study informed consent document.
Unexpected adverse events are those that are not described in the package insert or are not anticipated in the study informed consent document. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

The severity or grade of an adverse event may be measured using the following definitions:
Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.
Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.
Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention resolve

Adverse Event Reporting
The study will comply with the IRB & FDA reporting requirements and guidelines.

10. References:
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