Final Study Protocol and Statistical Analysis Plan

Study Title: Optimizing Preeclampsia Postpartum with POCUS (PPPOCUS): A Pilot Prospective Cohort Study
Primary Investigator: Ashten Waks, MD MSPH
Identifier: 7178 (NCT not yet assigned)
Date of Document Finalization: 7/21/2025

Project Details

Study Title:
Optimizing Preeclampsia Postpartum with POCUS (PPPOCUS): A Pilot Prospective Cohort Study

Lead Researcher/Investigator (https://research.uci.edu/human-research-protections/irb-application-process/lead-researcher-eligibility/):
Ashten Waks MD, MSPH

Enter the Lead Unit:
IR-7457-Obstetrics and Gynecology

Project Screener

Will this protocol be reviewed under a sIRB process?
No, there is no reliance involved. UCI will serve as the IRB of record.

Are the research procedures limited to the use/analysis of identifiable private information and/or identifiable biospecimens (no subject contact)?
No

Select the required level of review for this protocol:
Greater than Minimal Risk (Full Committee)

Check all sites where UCI investigator(s) will conduct research activities (e.g. recruitment, informed consent, and research procedures including accessing identifiable, private information about participants):
UCI Facilities or Sites (e.g. school, hospital or clinics, etc.)

Provide a non-technical summary of the project that can be understood by IRB/hSCRO members with varied research backgrounds, including non-scientists and community members (this summary should not exceed more than 250 words):
This study explores a novel approach to improving care for postpartum patients with preeclampsia, a pregnancy-related condition characterized by high blood pressure, protein in the urine, and organ dysfunction. Preeclampsia affects up to 9% of pregnancies and can progress to include complications of seizures, stroke, and even death. Over 60% of patients with preeclampsia continue to experience high blood pressure at the time of discharge from their delivery hospitalization, and many of these patients require blood pressure medications for up to 6 months postpartum. Even with blood pressure medications, many of these patients are readmitted to the hospital within six weeks of delivery.

In this study, we will utilize point-of-care ultrasound (POCUS), a quick and non-invasive, bedside imaging strategy, to look for signs of excess fluid accumulating in the lungs and venous system of postpartum patients with preeclampsia. Because excess fluid has the potential to worsen blood pressure, subjects with evidence of this on POCUS would be treated with a diuretic medication called furosemide (either orally or intravenously) within 24 hours of delivery.

Our main goal is to determine whether using POCUS can help physicians make better treatment decisions and improve short-term outcomes for postpartum patients with preeclampsia. We aim to achieve faster recovery of blood pressure, reduce the need for blood pressure medication at hospital discharge, and lower the rates of hospital readmission for those with preeclampsia. This study could significantly enhance the overall care and health of postpartum patients.

Type of Research

The purpose, specific aims, or objectives of the research is:
Biomedical

The research protocol is:
Investigator-initiated

Does the investigator-initiated study have any industry support?
No

Does this study include a Master Protocol or detailed project proposal?
Yes

Is this study an extension of a UCI IRB approved study (e.g., resubmission of ongoing exempt research; Open Label Extension) or is it otherwise related to a UCI IRB approved study?
No

Does this research meet the definition of a clinical trial that requires adherence to Clinicaltrials.gov?
Yes

If currently available, provide the CT.gov registration NCT # (Enter 8-digit sequence of numbers only):
Application to clinicaltrials.gov pending IRB approval

Study Funding

Select the funding source(s) (check all that apply):
Extramural funding (if this is an option)

Scientific/Scholarly Review

Is the research sponsor-initiated?
No

Data Safety Monitoring Plan

https://research.uci.edu/human-research-protections/clinical-research/data-and-safety-monitoring-for-clinical-research/

Does this protocol require a DSM plan?
Yes

Provide details of those individuals who will be responsible for the safety oversight of your protocol, including the relevant experience/expertise of each individual:
Afshan Hameed MD, MBA, Lead investigator, Health Sciences Clinical Professor, Department of Obstetrics & Gynecology and Cardiology, University of California, Irvine AND Ashten Waks MD MSPH, Co-investigator, Fellow Physician and incoming Health Sciences Assistant Clinical Professor, Department of Obstetrics & Gynecology, University of California, Irvine will have oversight of all subjects participating in the study and will monitor adverse events and/or unanticipated problems. Both Drs. Hameed and Waks have experience with safety oversight of prospective studies. Dr. Hameed is currently the lead investigator of UCI IRB #20195544 "Anticoagulation Profile in Pregnant Women treated with three times a day of Low Molecular Weight Heparin (LMWH)" and is primarily responsible for safety oversight of that study protocol. Dr. Waks is currently the lead fellow investigator of two IRB-approved studies in the Memorial Care system, "Acetylsalicylic Acid for Postpartum Preeclampsia (ASAPP): A Pilot Randomized Trial" and "Immediate Postpartum Glucose Tolerance Test: A Comparison with the Gold Standard", both of which she is oversees safety for as well.

Indicate how frequently accumulated protocol data will be reviewed and evaluated for participant safety, protocol conduct and progress, and, when appropriate, efficacy:
During and after completion of the study protocol for each patient, study personnel will be carefully monitoring for the safety outcome measures (hypotension, hypokalemia, acute kidney injury) described elsewhere in this document. These potential adverse events will be evaluated both by chart review and patient interview at the time of hospital discharge.

If any of these adverse events is detected, Drs. Hameed and Waks along with other relevant study personnel will be immediately notified. Study personnel will then reach out to the affected subject in person or by phone to obtain additional information. Depending upon the nature of the event, the study personnel will also work alongside the subject's primary obstetrician to provide available remedies (e.g. fluid resuscitation for hypotension, potassium repletion for hypokalemia). Any adverse event will subsequently be recorded in the study log and reported to the IRB within 1 week of occurrence.

Describe the events that would trigger an unscheduled review. Also include stopping guidelines and un-blinding rules if applicable:
An occurrence of any of the safety outcome measures would trigger an unscheduled review. Additionally, an interim safety analysis will be performed after 50% of the intended subjects (~ 48) have completed study participation. If more than 20% of the subjects enrolled and exposed to diuretic therapy are found to have experienced a specified safety outcome, premature termination of the study will be considered. If this occurs, the results will be submitted to the IRB for review.

List who will be locally monitoring and collecting information on adverse events and/or unanticipated problems (e.g., UCI Lead Researcher, Research Coordinator, etc.). Include the name, title and experience of the individual(s) and further describe each individual's role in the oversight of subject/patient participating in the protocol:
As above, Afshan Hameed MD, MBA, Lead investigator, Health Sciences Clinical Professor, Department of Obstetrics & Gynecology and Cardiology, University of California, Irvine AND Ashten Waks MD MSPH, Co-investigator, Fellow Physician and incoming Health Sciences Assistant Clinical Professor, Department of Obstetrics & Gynecology, University of California, Irvine will have

local oversight of all subjects participating in the study and will monitor adverse events and/or unanticipated problems.

Describe the plan for annual reporting of the participants' safety, and the protocol's conduct, progress, and efficacy, when appropriate:
In the absence of unanticipated adverse effects requiring urgent intervention, mild adverse safety outcomes will be reported to the IRB as part of the annual renewal progress report. Similarly, any protocol deviations, progress regarding recruitment, and updated efficacy data will be provided to the IRB as part of the annual renewal progress report as well.

If any of the following hazardous materials are involved in this research please check below:
N/A

Study Team

Co-Investigators: https://research.uci.edu/wp-content/uploads/study-team-tracking-log.xlsx

- Ashten Waks, MD, MSPH
- John Fox, MD
- Edmund Hsu, MD, MSIDT
- Xiang Feng, MD (maternal-fetal medicine fellow)
- Genevieve Mazza, MD (maternal-fetal medicine fellow)
- Devesh Naidoo, MD (maternal-fetal medicine fellow)
- Ann Nguyen Pham, MD (maternal-fetal medicine fellow)
- Katherine Bogaard, MD (obstetrics resident)
- Alessandra Rau, MD (obstetrics resident)
- Ọmọtayọ Balogun, MPH, MS2
- Emmanuella Tetteh, MS2
- Akira McDaniels, MS3
- Ellie Marlor, MS2
- Ciria Moya Fajardo, MS3

Background & Purpose of the Research

Describe the purpose, specific aims or objectives and specify the hypotheses or research questions to be studied:
The **purpose** of this study is to determine whether point-of-care ultrasound (POCUS) assessment of the lungs and inferior vena cava (IVC), both of which are a proxy for volume status, can be used to guide postpartum diuretic therapy in individuals with preeclampsia, and whether this strategy improves short-term maternal outcomes for this high-risk patient population.

Our **central hypothesis** is that, when guided by POCUS, use of diuretic therapy will improve postpartum outcomes in patients with preeclampsia relative to standard postpartum management alone. We will test our hypothesis by conducting a pilot prospective cohort study that addresses the following aims:

Specific Aim 1: Assess the feasibility of POCUS assessment of the lungs and IVC in postpartum patients with preeclampsia within 24 hours of delivery.

To date, only a small handful of studies has evaluated the role of POCUS in patients with preeclampsia, the most recent of which was presented at the Society for Maternal-Fetal Medicine's Annual Pregnancy Meeting in February of this year. This pilot study conducted at the University of Tennessee Health Science Center compared the median IVC collapsibility index in 12 participants with preeclampsia with severe features to that in 10 participants without hypertensive disorders of pregnancy. Although the researchers found no significant difference in median IVC collapsibility index between the study groups, the results suggest that POCUS assessment of the IVC is at least feasible in a newly postpartum patient.

Thus, with respect to this specific aim, we hypothesize that POCUS assessment will be able to successfully determine volume status in postpartum patients with preeclampsia. Specifically, we anticipate that POCUS can be reliably used to identify the presence of B-lines in the lungs and to measure the greatest IVC diameter and IVC collapsibility index.

Specific Aim 2: Determine whether use of POCUS assessment to guide diuretic administration improves postpartum outcomes, including persistent hypertension at hospital discharge, time to normotension, antihypertensive use at hospital discharge, and hospital readmission, among patients with preeclampsia.

With respect to this specific aim, we hypothesize that if oral or intravenous furosemide is administered to postpartum patients with preeclampsia following POCUS assessment that identifies 3 or more B-lines, an IVC diameter above 2cm, and/or an IVC collapsibility index less than 15%, there will be a decrease in persistent hypertension at hospital discharge (< 140/90 mm Hg and < 130/80 mm Hg), time to normotension, antihypertensive use at hospital discharge, and hospital readmission.

Provide the scientific or scholarly rationale for the research and describe the relevant background information and the specific gaps in current knowledge that this study intends to address:

Preeclampsia is a condition of the antenatal and postpartum periods, which manifests as new-onset hypertension and proteinuria. Globally, preeclampsia is estimated to affect up to 9% of all pregnancies, though as many as 63% of patients who receive this diagnosis will remain hypertensive beyond the time of postpartum hospital discharge. Because of this, up to 36% of patients with preeclampsia will require antihypertensive therapy at the time of hospital discharge, and between 26 – 74% of patients with preeclampsia will be readmitted during the first six weeks' postpartum. Cumulatively, these preeclampsia-related outcomes result in United States medical expenditures exceeding $36 million annually.

One proposed strategy for improving outcomes among patients with preeclampsia is postpartum administration of diuretics. This treatment is posited to target preeclampsia-related volume overload, which in turn is thought to contribute to continued hypertension in the postpartum period. The earliest trial on the use of diuretics for this purpose was published by Ascarelli et al in 2005 and involved randomization of 264 postpartum patients with preeclampsia to either a 5-day course of oral furosemide 20mg daily or standard preeclampsia management. Outcomes from this study included blood pressure changes over the postpartum hospital stay, need for antihypertensive therapy during hospitalization and at discharge, length of postpartum hospital stay, and other postpartum complications. While this intervention lowered systolic blood pressure by over 10 mm Hg in the first 48 hours postpartum, it did not result in a statistically significant decrease in antihypertensive therapy requirements, postpartum length of stay, or the frequency of other postpartum complications. As recently as 2021, Perdigao and colleagues published the FoR

BP trial, which similarly randomized 384 postpartum patients with hypertensive disorders of pregnancy to either a 5-day course of oral furosemide 20mg daily or standard preeclampsia management. Their primary outcomes were slightly different from the Ascarelli et al study and included persistent hypertension 7 days postpartum and days to resolution of hypertension. Ultimately, their results were more promising and demonstrated that a brief course of oral diuretics reduced the incidence of persistent hypertension by nearly 60% in patients with hypertensive disorders of pregnancy.

A potential explanation for this discrepancy in findings from earlier studies is that volume overload affects only a subset of patients with preeclampsia. While preeclamptic patients with volume overload are likely to demonstrate a meaningful response to diuresis, those without significant volume overload are less likely to respond to this treatment. Because the aforementioned studies did not account for patients' volume status at the time of randomization or diuretic administration, it seems possible that they did not sufficiently capture the patient population most likely to respond to the intervention of interest.

With regards to evaluating postpartum volume status and how it might relate to diuretic response, most obstetric practitioners currently rely on findings from physical examination (e.g. jugular venous distension, rales on lung exam, peripheral edema) that are known to have limited sensitivity. However, there is increasing evidence in the obstetric literature that use of POCUS might be a helpful adjunct for determining postpartum volume status. In 2023, Chong et al conducted a prospective cohort study of 31 patients who experienced at least 500mL blood loss during vaginal delivery. The investigators used POCUS to assess the IVC collapsibility index during the first, second, and third stages of labor as well as at the time of bleeding and following rapid resuscitation with 500mL of intravenous fluids. They then compared these indices to heart rate and mean arterial pressure at the same intervals and found that the IVC collapsibility index demonstrated more variation in response to volume status than did either heart rate or mean arterial pressure, both of which instead remained relatively stable over time. Moreover, a review of POCUS' role in monitoring the response to postpartum volume resuscitation was published in the *American Journal of Obstetrics & Gynecology* in 2024. This review suggested that the presence of three or more B-lines per screen on lung ultrasound is indicative of pulmonary edema during pregnancy and the postpartum period, as B-lines develop when air content in the lungs is replaced by transudate or exudate in the interstitium. It further suggested that an enlarged IVC diameter (> 2.0 cm) or minimal IVC collapsibility index (<15%) identified on POCUS could also be used to determine volume overload antenatally and postnatally.

As stated above, the proposed study aims not only to confirm the feasibility of POCUS for this purpose, but also to demonstrate how POCUS could be used to amplify the equivocal success of diuretic therapy for improving postpartum outcomes in patients with preeclampsia.

Provide relevant preliminary data (animal and/or human):

As above

Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims:

Primary outcomes variables:

- Persistent hypertension at time of postpartum hospital discharge, defined both as blood pressure > 140/90 mm Hg according to ACOG guidelines and 130/80 mm Hg according to JNC-9 guidelines
- Days to resolution of hypertension, defined both as blood pressure < 140/90 mm Hg according to ACOG guidelines and 130/80 mm Hg according to JNC-9 guidelines

Secondary maternal outcome variables:

- Need for antihypertensive at postpartum hospital discharge
- Addition of second antihypertensive agent during postpartum hospitalization
- Length of postpartum hospital stay
- Readmission for blood pressure control within 30 days of discharge from initial postpartum hospitalization
- Feasibility for future study, defined both as the number of subjects enrolled divided by the number of subjects with either POCUS lung or IVC ultrasound images collected within 24 hours of delivery and as reliability between image assessment as performed by study staff and by blind reviewer

Secondary safety outcome variables:

- Hypotension, defined as blood pressure < 90 mm Hg systolic and/or < 60 mm Hg diastolic
- Tachycardia, defined as heart rate > 100 beats per minute
- Moderate or severe hypokalemia, defined as potassium < 3.0 mEq/L
- Acute kidney injury, defined as creatinine > 1.1 mg/dL

Predictor variables

- Maternal age at delivery
- Gravidity and parity
- Self-reported race/ethnicity
- Body mass index at time of delivery admission
- Weight at time of delivery admission
- Preeclampsia diagnosis (preeclampsia without severe features, preeclampsia with severe features, HELLP syndrome, eclampsia)
- History of preeclampsia in a previous pregnancy
- Pregestational diabetes
- Gestational diabetes
- Autoimmune disease
- Renal disease
- Multiple gestation
- Conception via in vitro fertilization
- Antenatal low-dose aspirin use
- Antenatal betamethasone exposure
- Antenatal magnesium sulfate exposure
- Gestational age at delivery
- Mode of delivery
- Quantified blood loss at delivery
- Physical exam findings consistent with volume overload (jugular venous distension, rales on pulmonary exam, peripheral edema)
- Presence of 3 or more B-lines on POCUS lung ultrasound within 24 hours of delivery
- Presence of maximum IVC diameter > 2cm on POCUS within 24 hours of delivery
- Presence of IVC collapsibility index (maximum IVC diameter – the minimum IVC diameter divided by the maximum IVC diameter) < 15% on POCUS within 24 hours of delivery
- Maximum systolic blood pressure during each day of postpartum hospitalization (mm Hg)

- Maximum diastolic blood pressure during each day of postpartum hospitalization (mm Hg)
- Maximum systolic blood pressure at hospital discharge (mm Hg)
- Maximum diastolic blood pressure at hospital discharge (mm Hg)
- Daily weight during each day of postpartum hospitalization (kg)
- 24-hour net fluid status (intake – output) following baseline POCUS assessment (mL)

Comparison groups

- Group 1: Historical matched controls
    - A retrospective cohort comprised of patients who delivered before implementation of POCUS-guided postpartum management of preeclampsia (1/1/2024 - 6/1/2025). These patients will be selected from the electronic medical record and matched to enrolled patients according to age, body mass index, gestational age at delivery, severity of preeclampsia, and mode of delivery.
- Group 2: POCUS-guided subjects receiving oral furosemide
    - A prospective cohort of patients diagnosed with preeclampsia who will be enrolled and undergo POCUS within 24 hours of delivery. Those meeting pre-specified hemodynamic criteria ($\geq$ 3 B-lines, maximum IVC diameter > 2 cm, and/or IVC collapsibility index < 15%) will receive a 5-day course of oral furosemide 20mg and oral potassium chloride 40mEq daily.
- Group 3: POCUS-guided subjects receiving intravenous furosemide
    - A prospective cohort of patients diagnosed with preeclampsia who will be enrolled and undergo POCUS within 24 hours of delivery. Those meeting pre-specified hemodynamic criteria ($\geq$ 3 B-lines, maximum IVC diameter > 2 cm, and/or IVC collapsibility index < 15%) will receive a single dose of intravenous furosemide 40mg and oral potassium chloride 40mEq.

List up to ten relevant references/articles to support the rationale for the research:

1. Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 222. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2020;135:e237-60.
2. Ditisheim A, Wuerzner G, Ponte B, et al. Prevalence of hypertensive phenotypes after preeclampsia: A prospective cohort study. *Hypertension* 2018;71:103-109.
3. Stevens W, Shih T, Incerti D, et al. Short-term costs of preeclampsia to the United States health care system. *Am J Obstet Gynecol* 2017; 217:237-47.3.16.
4. Balhotra K, Roach C, Al-Kouatly H, et al. Association of antihypertensive medication at discharge with readmission for postpartum preeclampsia. *Am J Obstet Gynecol* 2023;228(6):747-748.
5. Ascarelli MH, Johnson V, McCreary H, et al. Postpartum preeclampsia management with furosemide: a randomized clinical trial. *Obstet Gynecol* 2005;105(1):29-33.
6. Lopes Perdigao J, Lewey J, Hirshberg A, et al. Furosemide for accelerated recovery of blood pressure postpartum in women with a hypertensive disorder of pregnancy: A randomized controlled trial. *Hypertension* 2021;77(5):1517-1524.
7. Chong Y, Yu Y, Zhao Y, et al. Value of inferior vena cava diameter and inferior vena cava collapse index in the evaluation of peripartum volume: A prospective cohort study. *Eur J Obstet Gynecol Reprod Biol* 2023;285:69-73.
8. Martins JG, Saad A, Saade G, Pacheco LD. The role of point-of-care ultrasound to monitor response of fluid replacement therapy in pregnancy. *Am J Obstet Gynecol* 2024;231(6):563-573.

9. Parra E, Brackney K, Piersall L, et al. (2025, January 26 – February 1). (1024) Comparing inferior vena cava collapsibility in postpartum patients with and without severe preeclampsia. Society for Maternal-Fetal Medicine 2025 Pregnancy Meeting, Denver, CO, United States.
10. Ambrozic J, Brzan Simenc G, Prokselj K, et al. Lung and cardiac ultrasound for hemodynamic monitoring of patients with severe pre-eclampsia. *Ultrasound Obstet Gynecol* 2017;49(1):104-109.

Subject Population(s) (Individuals/Records/Biospecimens)

Check all subject populations/data sources that apply to the research:
Adults Competent to Provide Informed Consent
UCI Inpatients or Outpatients (Receiving Diagnosis/Treatment/Surgery)
UCI Students/Staff/Faculty
Use of identifiable or coded data, specimens, records, charts

Maximum and Expected Number of Persons/Records/Biospecimens to be Enrolled:
Specify the maximum and expected numbers of individual-level information and/or biospecimens to be accessed/analyzed within each Category/Group

- Group 1: Historical matched controls (N = 48)
- Group 2: POCUS-guided subjects receiving oral furosemide (N = 48)
- Group 3: POCUS-guided subjects receiving oral furosemide (N = 48)

Will this study only take place at UCI and does not involve other sites?
Yes

Eligibility Factors (Inclusion/Exclusion Criteria):
Inclusion criteria:
Historical cohort (group 1):

- Age greater than or equal to 18 years at the time of delivery
- Diagnosis of preeclampsia (without severe features, with severe features, HELLP syndrome, eclampsia) during pregnancy
- Gestational age greater than or equal to 20 weeks' gestation at delivery
- Delivery at the study institution within the 18-month period prior to implementation of the study POCUS intervention
- Available and complete postpartum clinical data on:
    - Daily blood pressure
    - Antihypertensive use
    - Length of postpartum hospital stay
    - Readmission within 30 days of primary hospitalization

Prospective cohorts (groups 2 and 3):

- Age greater than or equal to 18 years at the time of enrollment
- Diagnosis of preeclampsia (without severe features, with severe features, HELLP syndrome, eclampsia) made up until 24 hours postpartum
- Postpartum and within 24 hours of delivery
- Able to provide informed consent in English

Exclusion criteria:
Historical cohort (group 1):

- Delivery at an outside facility or incomplete postpartum records available for analysis

- Pre-existing diagnosis of chronic hypertension; selected to mirror prospective cohort exclusion criteria (see below)
- Documentation of chronic kidney disease (CKD stage 3 or higher); selected because diuresis is more likely to be avoided in this patient population even in the presence of physical exam findings suggesting volume overload.
- Documentation of postpartum complications unrelated to preeclampsia that may significantly alter hemodynamics (e.g., sepsis, postpartum hemorrhage); selected because diuresis is more likely to be avoided in this patient population even in the presence of physical exam findings suggesting volume overload.

Prospective cohorts (groups 2 and 3):

- Pre-existing diagnosis of chronic hypertension; selected because previous studies on furosemide use in patients with postpartum preeclampsia have found a significant reduction in hypertension among patients with newly diagnosed hypertensive disorders of pregnancy, but not among those with pre-gestational hypertension (Maykin et al, 2024), meaning that inclusion of this population might reduce the magnitude of study effects.
- Baseline renal dysfunction with serum creatinine > 1.1 mg/dL; selected as this laboratory finding has been pre-selected as a safety outcome.
- Baseline hypokalemia with serum potassium < 3.5 mEq/L despite previous repletion with intravenous or oral potassium chloride; selected as this laboratory finding has been pre-selected as a safety outcome.
- Known hypersensitivity to furosemide or sulfa drugs; selected because this would preclude exposure to the study medication of interest.
- Current use of diuretics for other indications (e.g. heart failure); selected because this may require a furosemide or other diuretic regimen different from that planned for the study intervention.

Subpart B - Pregnant Women & Neonates

Will your research involve pregnant women or fetuses?

No – patients will not be eligible to participate in the study until after they have delivered.

Pre-Screening and Determining Eligibility without Informed Consent

Will Identifiable information be obtained for the purpose of screening, recruiting, or determining eligibility of prospective subjects?

Yes

Provide a complete list of the data points, variables, and/or information that will be collected during Pre-Screening (i.e. data abstraction form):
Or specify variables or information required for Pre-Screening:

- Maternal age at delivery
- Gestational age at delivery
- Preeclampsia status
- Documentation of pre-existing chronic hypertension
- Current medications used
- Medication allergies
- Baseline creatinine
- Baseline potassium

Check all the Pre-Screening activities that apply:

- Study team will obtain information through oral or written communication with the prospective subject or LAR (i.e. self-report of medical information; medical records will not be screened)
- Study team will screen medical records to determine subject eligibility

Select Medical Record Source (check all that apply):

- Study team will access their own UCI patients' records and abstract data directly from those records

Will the study team screen stored identifiable biospecimens?
No

Will the study team contact subjects for eligibility or recruitment purposes?
Yes. As stated above, patients admitted to UC Irvine Medical Center's postpartum unit with a diagnosis of preeclampsia will be identified via a combination of chart review and notification by the patient's primary obstetrician. Study personnel will conduct further chart reviews of and interviews with identified patients to confirm eligibility. All patients meeting the above diagnostic and inclusion criteria will be approached by study personnel for enrollment.

Recruitment Methods

Will this study involve NO direct contact with participants (i.e., passive observation of public behavior)?
No

Indicate all methods that will be used to recruit subjects for this study:

- Clinicaltrials.gov
- Colleagues provide subjects with information about the research and how to contact investigators
- Colleagues seek or obtain the subjects' permission for investigators to contact them
- Study team will approach subjects who are vulnerable to undue influence or coercion (i.e. students, employees and patients)

Informed Consent Process

Consent Forms: https://research.uci.edu/human-research-protections/research-subjects/informed-consent/drafting-the-informed-consent-form/

- Template: https://research.uci.edu/human-research-protections/irb-forms/

Does this study involve the creation, use, or disclosure of Protected Health Information (PHI)?
Yes

Identify the HIPAA authorization process (Check all that apply):

- Partial waiver of HIPAA authorization for screening/recruitment purposes only
- Signed authorization obtained prior to further access to PHI
- Signed HIPAA authorization obtained

Identify the consent or assent process as applicable for each participant population (check all that apply):

- Paper-based signed informed consent/assent

Indicate the location where the consent process will take place (check all that apply):

- Private room

Specify how the research team will assure that subjects, their parents, or their legally authorized representative (LAR) have sufficient time to consider whether to participate in the research:

Prospective subjects will be approached by study personnel as early in their postpartum course as possible. After a discussion of the study, a hard copy of the consent form will be left with the prospective subject for review. The prospective subject will have up to 24 hours from the time of delivery to review the consent documentation before definitively deciding whether to participate. As subjects must be enrolled and evaluated within the first 24 hours postpartum, a longer duration for consideration is not feasible.

What type of consent process will be used for Non-English Speaking Participants?

For the purposes of this pilot study, only English speakers will be consented and enrolled. If the results from this pilot are promising, we intend to expand on this study and to include non-English speaking participants in the future.

When a partial waiver is requested, the Lead Researcher is requesting the HIPAA research authorization be waived for a portion of the study, such as a waiver for subject identification or recruitment purposes.

Please specify for what purpose the partial waiver is requested:

A partial waiver has been requested to allow for pre-screening of potential subjects. All patients admitted to the postpartum service would undergo this pre-screening. Pre-screening would specifically include electronic medical record-based review of the key inclusion and exclusion criteria, including preeclampsia status, gestational age at delivery, body mass index at time of delivery admission, documentation of pre-existing chronic hypertension, current medications used, medication allergies, baseline creatinine, and baseline potassium.

Does the use or disclosure of personal health information involve more than minimal risk?

No

Would the granting of the waiver adversely affect privacy rights and welfare of the individuals whose records will be used or disclosed?

No

Explain (justify) the answer:

Pre-screening information would be available only to study personnel. Additionally, none of the information garnered during the pre-screening process would be recorded in study logs until consent was obtained later in the recruitment process.

Could the research practicably be conducted without a waiver of HIPAA authorization?

No

Explain the answer:

Patients' personal health information must be accessed to identify potential subjects for recruitment. It would not otherwise be feasible or practical to request that all patients admitted to the postpartum unit sign a HIPAA Authorization form allowing access to their medical records so that investigators could then identify which patients meet the inclusion criteria.

Could the research practicably be conducted without access to, use or disclosure of the personal identifiers listed in the PHI question?
No

Explain the answer:
As above, patients' personal health information must be accessed to identify potential subjects for recruitment. It would not otherwise be feasible or practical to request that all patients admitted to the postpartum unit sign a HIPAA Authorization form allowing access to their medical records so that investigators could then identify which patients meet the inclusion criteria.

Are the privacy risks reasonable relative to the anticipated benefits of the research?
Yes

Describe the risk/benefit analysis performed to explain the answer above:
The risks of breach of confidentiality are low, and the benefits of study participation would likely outweigh the risks of accessing the medical records or of breach of confidentiality. The information obtained would enable us to identify postpartum patients with preeclampsia whose assessment may be enhanced with POCUS, but who otherwise would not receive this evaluation under the current standard of care.

Describe the plan to protect the personal identifiers from improper use and disclosure (i.e., describe data security methods):
The name of and any relevant pre-screening information for eligible patients would be kept only until the patient makes a decision regarding participation. If the patient signs the consent form and HIPAA authorization required to participate, any personal health information recorded in the secure Redcap study log would be de-identified and associated only with the patient's given subject number. If the patient chooses not to participate, her name and any relevant pre-screening information would be promptly destroyed.

Describe the plan to destroy the personal identifiers at the earliest opportunity, or provide a health or research justification for retaining the identifiers:
Once an enrolled subject has completed the study protocol and all required information has been collected, that subject's personal health information would be de-identified in secure Redcap study logs. This is anticipated to occur approximately 30 days from the time of study enrollment, as all subjects will be followed for this duration to assess for the secondary outcome of hospital readmission. After completion of the study and once the findings have been presented/published, all the retained de-identified information would be permanently destroyed.

Describe how potential subjects will be identified:
Potential subjects would be identified through one of two strategies. First, the obstetric team caring for the postpartum unit may notify study personnel of a potential subject. After notification, study personnel would then complete pre-screening through the electronic medical record to ensure that the potential subject was eligible before approaching that person for further discussion

of the study. Second, study personnel would complete a daily review of the list of patients admitted to the postpartum unit and then proceed with pre-screening for all potential subjects documented to have preeclampsia.

Research Procedures

Check all boxes that apply to the research:

- Analysis of Existing Identifiable or Coded Data, Specimens, Records, Charts, and Datasets
- Collection of Blood Samples (Venipuncture)
- Surveys/Questionnaires/Interviews/Oral Histories
- Option for imaging?

Indicate the phase(s) of the study, if applicable:
N/A
Will deception or incomplete disclosure be involved in the research?
No

Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme:
This will be a pilot prospective cohort study of postpartum patients with preeclampsia. Subjects will not be randomized to a particular intervention, instead the need for the study intervention (diuretic therapy) will be predicated on the subjects' own POCUS findings. As this is not a randomized controlled trial, there is no proposed randomization, stratification, or blinding scheme.

Notably, the intervention will change after the first cohort of 48 subjects has completed study participation. This first cohort (group 2) will receive a 5-day course of oral furosemide 20mg daily and potassium chloride 40mEq daily. The second cohort (group 3) will receive a one-time dose of intravenous furosemide 40mg and oral potassium chloride 40mEq. The 5-day course of oral furosemide was selected as a study intervention to facilitate comparison of our results with those of previous studies on the role of diuretics in managing postpartum preeclampsia, the majority of which have relied on this administration and dosing schedule.[5,6] The single dose of intravenous furosemide was selected as a more pragmatic study intervention, as this is the treatment most frequently given in our postpartum unit when preeclamptic patients are suspected to have persistent hypertension related to volume overload. While not yet rigorously evaluated in the obstetric literature, this practice is supported by Maykin et al's 2024 study, which demonstrated that a single dose of intravenous furosemide 40mg significantly reduced systolic blood pressure within 2 hours of administration among patients with hypertensive disorders of pregnancy requiring antihypertensive therapy.

Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived:
Subjects' active participation in the study will conclude at the time of discharge from their postpartum hospitalization or on completion of their furosemide course, whichever is the later of the 2 endpoints. However, enrolled subjects will also consent to have their medical records

passively reviewed for up to 30 days from the time of discharge, as hospital readmission during this interval is a secondary study outcome.

The primary outcomes of persistent hypertension at the time of postpartum hospital discharge and days to resolution of hypertension will both be assessed at the abovementioned endpoints. Persistent hypertension at the time of postpartum hospital discharge will be assessed as a dichotomous variable, while days to resolution of hypertension will be assessed as both a continuous and categorical variable (0 days, 1 day, 2 days, 3 + days). Neither of these primary outcomes will be a composite variable.

Describe the statistical methods for the stated specific aims and hypotheses. Your analysis plans should match the stated study specific aims and hypotheses:

For **Specific Aim 1** (assess the feasibility of POCUS assessment of the lungs and IVC in postpartum patients with preeclampsia within 24 hours of delivery), two different feasibility calculations will be performed. The first calculation will entail dividing the number of subjects enrolled by the number of subjects with adequate POCUS lung or IVC ultrasound images collected within 24 hours of delivery. The second calculation will be a measure of inter-rater reliability between image assessment as performed by general study personnel and by blind reviewer. The blind reviewer will be tasked with evaluating each image deemed "abnormal" (> 3 B-lines on lung ultrasound, IVC diameter > 2cm, OR IVC collapsibility index < 15%) by the study personnel performing the ultrasound. Inter-rater reliability of this assessment will be determined using both percent agreement and Cohen's Kappa statistic.

For **Specific Aim 2**, (determine whether use of POCUS assessment to guide diuretic administration improves postpartum outcomes), the primary outcomes of persistent hypertension at the time of postpartum hospital discharge and days to resolution of hypertension will be treated as a dichotomous variable and as a time to event analysis using Kaplan-Meier survival curves, respectively. Chi-squared tests of independence will be used to compare the dichotomous variable between both intervention groups and the historic control group. In the event the results are statistically significantly different between the 3 groups, Bonferroni adjustment and/or paired comparisons will be performed pending the distribution of the data to pinpoint the exact differences between each group. Log-rank tests will be used to compare the Kaplan-Meier survival curves between both intervention groups and the historic control group.

Secondary outcomes of the need for antihypertensive therapy at postpartum hospital discharge, addition of a second antihypertensive agent during the postpartum hospitalization, length of postpartum hospital stay, and readmission for blood pressure control within 30 days of initial discharge will all be treated as dichotomous variables. Similarly, safety outcomes of hypotension, tachycardia, moderate or severe hypokalemia, and acute kidney injury will also be treated as dichotomous variables. As above, these dichotomous variables will be compared between both intervention groups and the historical control group using Chi-squared tests of independence, with application of Bonferroni adjustment or paired comparisons as appropriate based on the distribution of the data. Finally, the remaining secondary outcome of change in BNP levels from the time of study enrollment through hospital discharge will be treated as a continuous variable. This continuous variable will be compared between both intervention groups and the historical control group using one-way ANOVA, with application of Bonferroni adjustment or paired comparisons as appropriate based on the distribution of the data.

Describe the statistical method(s) that will be used to analyze the primary outcome(s) or endpoints:

As above, the primary outcomes of persistent hypertension at the time of postpartum hospital discharge and days to resolution of hypertension will be treated as a dichotomous variable and as a time to event analysis using Kaplan-Meier survival curves, respectively. Chi-squared tests of independence will be used to compare the dichotomous variable between both intervention groups and the historic control group. In the event the results are statistically significantly different between the 3 groups, Bonferroni adjustment and paired comparisons will be performed to

pinpoint the exact differences between each group. Log-rank tests will be used to compare the Kaplan-Meier survival curves between both intervention groups and the historic control group.

If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis and if necessary, provide a breakdown of the methods used per outcome or endpoint:
We plan on completing sub-group analyses to further evaluate Specific Aim 2 according to mode of delivery, gestational age at which preeclampsia was diagnosed, patient-reported race/ethnicity, body mass index, and pre-existing risk factors for preeclampsia. Mode of delivery will be defined as either vaginal delivery or cesarean delivery. The gestational age at which preeclampsia was diagnosed will be defined as either early-onset (< 34 weeks' gestation) or late-onset (> 34 weeks' gestation). Race/ethnicity will be defined as White, Hispanic, non-Hispanic Black, Asian/Pacific Islander, and other. Body mass index will be defined as either obese ($\geq$ 30 kg/m^2), overweight (25 29.9 kg/m^2), or normal (< 25 kg/m^2). Pre-existing risk factors for preeclampsia will be defined as history of preeclampsia in a prior pregnancy, pregestational diabetes mellitus, renal disease, autoimmune disease, and multifetal gestation.

Sample Size Determination: Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint:
As previously reported in the literature, the prevalence of persistent postpartum hypertension in patients with hypertensive disorders of pregnancy is roughly 35% (Lopes Perdigao et al, 202). To find a 70% reduction in persistent postpartum hypertension between the intervention and historical cohorts, which is the maximum effect size identified in earlier studies on postpartum diuretic use, at a two-sided alpha of 0.05 and power of 0.8, we would require 43 subjects per study arm. Accounting for 10% non-adherence to study protocols either due to inability to obtain accurate POCUS images or subject declination of recommended medications, we would require 48 subjects per arm or 144 subjects total. Only 96 of these would be recruited, as the remaining 48 would be selected from the historical cohort generated using the electronic medical record.

Provide a detailed chronological description of the clinical or treatment plan:
Eligible patients will be approached by study personnel within the first 24 hours postpartum. Prior to this, eligible patients will have undergone a screening comprehensive metabolic panel to ensure that their baseline creatinine and potassium meet study standards (note: a comprehensive metabolic panel is obtained in all patients with preeclampsia to determine the severity of the condition, so this blood draw is already part of routine preeclampsia care). During the preliminary discussion regarding study participation, eligible patients will be provided with a copy of the consent form and advised that consent is completely voluntary and will not otherwise affect their care. Patients providing informed consent will then be assigned a study identification number. The study staff member who obtains consent will subsequently elicit a detailed history focused on the predictor variables outlined earlier in this document as well as perform a physical exam focused on signs of volume overload (e.g. jugular venous distension, rales on lung exam, peripheral edema). At this time, a baseline brain natriuretic peptide (BNP) level, which is another proxy for volume status, will also be collected for all subjects. This information, in addition to baseline laboratory findings, weight, and vital signs, will be entered directly into a secure Case Report Form in the study's Redcap database.

During the consent encounter, the study staff member who obtains consent will also perform POCUS of the lungs and the IVC. All POCUS assessments will be performed using either the curvilinear or phased array settings on a portable Butterfly IQ+™ ultrasound system. Images obtained via the Butterfly IQ +™ ultrasound system will be labeled according to the subject's unique identification number and transmitted directly to a digital study archive.

Any subject who is found to have 3 or more B-lines, a maximum IVC diameter above 2.0cm, or an IVC collapsibility index less than 15% on POCUS will become a candidate for diuretic therapy, which will be ordered by the patient's primary inpatient provider. The first cohort of 48 patients will be treated with oral furosemide 20mg daily and oral potassium chloride 40mEq daily for a total of 5-days. As patients delivered vaginally are typically discharged 2-3 days after birth and delivered via cesarean are typically discharged 4-5 days after birth, patients who have not yet completed the medication course by the time of planned discharge will be prescribed the remainder of their medications before departing the hospital. The second cohort of 48 patients will be treated with a single dose of intravenous furosemide 40mg and oral potassium chloride 40mEq on postpartum day 1. Regardless of assigned cohort, all subjects prescribed diuretic therapy will have a repeat POCUS approximately 24 hours after receiving their first dose of the medication to assess for change in the number of B-lines, maximum IVC diameter, and/or IVC collapsibility index. After receipt of their diuretic therapy and completion of a follow-up POCUS, subjects with the abovementioned evidence of volume overload will receive standard management of their preeclampsia.

Any subject who is NOT found to have 3 or more B-lines, a maximum IVC diameter above 2.0cm, or an IVC collapsibility index less than 15% on POCUS will receive only standard management of her preeclampsia. Standard management of preeclampsia entails serial blood pressure measurement as frequently as every 15 minutes for values consistent with severe hypertension (> 160/110 mm Hg) and every 6 hours for values consistent with normotension or mild hypertension (< 160/110 mm Hg). Patients with severe hypertension will be managed according to current inpatient protocols. Patients with mild hypertension (140 – 159/90 – 109 mm Hg) will be managed according to the following algorithm:

- If more than 50% of BP are > 150/100 mm Hg, begin extended-release nifedipine 30mg by mouth daily
- If, after 24 hours following medication initiation, more than 50% of BP remain > 150/100 mm Hg, increase the dose of extended-release nifedipine to 60my by mouth daily. This step can be repeated until a maximum daily dose of extended-release nifedipine 120mg by mouth is reached
- If more than 50% of BP are > 150/100 mm Hg once the maximum daily dose of extended-release nifedipine 120mg by mouth is reached, begin labetalol 200mg by mouth twice daily
- If, after 24 hours following the initiation of labetalol, more than 50% of BP remain > 150/100 mm Hg, increase the dose to labetalol 400mg by mouth twice daily. This step can be repeated until a maximum daily dose of labetalol 2400mg by mouth is reached

In addition to the above, each subject enrolled in the study will have strict daily weights and intake/output documented for every 24-hour period of her hospitalization. Prior to discharge, each subject enrolled in the study will have a repeat BNP level as well as a comprehensive metabolic

panel to assess for safety outcomes including acute kidney injury and moderate to severe hypokalemia. All subjects will be candidates for discharge home beginning on postpartum 2 day if their blood pressure has been at goal (< 150/100 mm Hg) for at least 12 hours. As is the current standard of care, all patients will be advised to have an outpatient blood pressure check within 72 hours of hospital discharge; however, this visit will not be considered as part of the study protocol.

Although subjects' in-person participation will be complete at the time of hospital discharge or when they have completed their assigned diuretic course (whichever is later), they will also be consented for chart review of the clinical and safety outcomes through 30 days postpartum. Once every subject has reached 30 days postpartum, the study will be deemed complete. At that time, all de-identified POCUS images will be obtained from the digital study archive and blindly reviewed by the lead investigator. As described with the statistical considerations for Specific Aim 1, these images will be specifically reviewed for reliability in the findings consistent with volume overload (≥ 3 B-lines, a maximum IVC diameter ≥ 2.0cm, or an IVC collapsibility index < 15%).

Specify the total duration of a subject's participation in the study and clearly outline the duration of participation for each study visit and sub-study, as applicable:
Subjects' in-person participation will be complete at the time of hospital discharge or when they have completed their assigned diuretic course (whichever is later), though they will also be consented for chart review of the clinical and safety outcomes through 30 days postpartum. On average, participation is anticipated to occur over a 2-to-5-day period.

Will this study require clinical items/ services from UC Irvine Health?
Yes

List the research procedure (e.g. phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, lumbar punctures, MRIs, CT Scans), and identify the unit/department that will perform the procedure:
Prescribed diuretics will be dispensed by the inpatient pharmacy; this is not expected to increase our pharmacy colleagues' responsibilities because these medications are already being regularly dispensed to our postpartum population. Daily weights, strict intake/output, and vital signs will be measured and documented by the postpartum registered nursing staff. Required blood draws will be performed either by the postpartum registered nursing staff and/or inpatient phlebotomists.

Does the research involve the use of identifiable private information?
Yes

Indicate the types/sources of identifiable private information (Check all that apply):
UCI Health Medical Records

Indicate whether the information was originally collected for research purposes:
No

Explain how the information were originally collected (e.g., clinical care):
Clinical care

Provide a complete list of the data points, variables, and/or information that will be collected (i.e. data abstraction form):

- Maternal age at delivery
- Gravidity and parity
- Self-reported race/ethnicity
- Body mass index at time of delivery admission
- Weight at time of delivery admission
- Preeclampsia diagnosis (preeclampsia without severe features, preeclampsia with severe features, HELLP syndrome, eclampsia)
- Gestational age at which preeclampsia was diagnosed
- Documentation of pre-existing chronic hypertension
- History of preeclampsia in a previous pregnancy
- Pregestational diabetes
- Gestational diabetes
- Autoimmune disease
- Renal disease
- Multiple gestation
- Conception via in vitro fertilization
- Antenatal low-dose aspirin use
- Antenatal betamethasone exposure
- Antenatal magnesium sulfate exposure
- Current medications
- Medication allergies
- Gestational age at delivery
- Mode of delivery
- Quantified blood loss at delivery
- Baseline creatinine and date
- Baseline potassium and date
- Baseline BNP and date
- Physical exam findings consistent with volume overload (jugular venous distension, rales on pulmonary exam, peripheral edema)
- Presence of 3 or more B-lines on POCUS lung ultrasound within 24 hours of delivery
- Presence of maximum IVC diameter > 2cm on POCUS within 24 hours of delivery
- Presence of IVC collapsibility index (maximum IVC diameter – the minimum IVC diameter divided by the maximum IVC diameter) < 15% on POCUS within 24 hours of delivery
- Maximum systolic blood pressure during each day of postpartum hospitalization (mm Hg), with recorded dates
- Maximum diastolic blood pressure during each day of postpartum hospitalization (mm Hg), with recorded dates
- Maximum systolic blood pressure at hospital discharge (mm Hg), with recorded dates
- Maximum diastolic blood pressure at hospital discharge (mm Hg), with recorded dates
- Daily weight during each day of postpartum hospitalization (kg), with recorded dates
- 24-hour net fluid status (intake – output) following baseline POCUS assessment (mL), with recorded dates
- Presence of 3 or more B-lines on POCUS lung ultrasound within 24 hours of diuresis (for subjects receiving this therapy)

- Presence of maximum IVC diameter > 2cm on POCUS within 24 hours of delivery (for subjects receiving this therapy)
- Presence of IVC collapsibility index (maximum IVC diameter – the minimum IVC diameter divided by the maximum IVC diameter) < 15% on POCUS within 24 hours of delivery (for subjects receiving this therapy)
- Follow-up creatinine and date
- Follow-up potassium and date
- Follow-up BNP and date
- Length of hospitalization
- Hospital readmission within 30 days of delivery, with recorded dates

Specify the time-frame of the data to be accessed (e.g. January 2002 to 2024):
Clinical data will be assessed for a total of 10 months (duration of pregnancy and postpartum period)

This study will use medical records, indicate the source:
Study personnel will access their own UCI patients' records and abstract data directly from those records.

Does the research involve the use of identifiable biospecimens?
No

Will individual results be shared with subjects?
Yes

Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician):
Study personnel will discuss POCUS results as well as their clinical significance with each subject. These results will also be disclosed to the patient's primary inpatient provider, as this provider will be instructed to order indicated diuretic therapy. Any subsequent abnormal laboratory finding or vital sign attributed to study participation will also be disclosed to subjects by a physician on the study team.

Explain what information will be shared and how the results will be shared:
As above, information regarding POCUS findings, laboratory results, and vital signs will be made available to subjects. This information will be shared directly and verbally by study personnel, the patient's primary inpatient provider, or a combination of the two.

Will overall study results will be shared with subjects?
Subjects will be directed to clinicaltrials.gov to review overall study results.

Risk Assessment

Describe and assess any reasonably foreseeable risks and discomforts associated with each procedure for each subject population — physical, psychological, social, legal or other:
Overall, the study as described is thought to be of minimal risk, as the proposed intervention (diuretic therapy) is already in use among select patients during the postpartum period. Nonetheless, as with participation in any clinical research study, there is the potential risk of a

breach in confidential, protected health information (PHI). Additionally, there are theoretical physical risks associated with POCUS, diuretic therapy, and general study participation including:

- Discomfort associated with POCUS
- Discomfort associated with necessary lab draws
- Medication hypersensitivity
- Hypertension
- Tachycardia
- Hypokalemia
- Acute kidney injury
- Polydipsia
- Headaches
- Mental confusion
- Muscle aches or weakness
- Heart rhythm disturbances

Numerous randomized controlled trials have been performed to assess both the efficacy and safety of a brief course of diuretic therapy during the postpartum period. None of these studies have found an increased risk of hypokalemia, acute kidney injury, polydipsia, headaches, mental confusion, muscle aches or weakness, or heart rhythm disturbances among patients treated with diuretics postpartum. Moreover, none of these studies have found an increased risk of more general severe maternal morbidity, including infection or delayed postpartum hemorrhage, in patients exposed to this therapy postpartum (Ascarelli et al, 2017; Lopes Perdigao et al, 2021). Beyond this, hypersensitivity or allergic reaction to furosemide is thought to be rare, affecting less than 0.5% of exposed individuals regardless of recent pregnancy status (Shteinberg et al, 2007).

If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality:

The research team, authorized UCI personnel, and regulatory entities such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) may have access to subjects' study records and will collaborate to protect the safety and welfare of all subjects. While the research team will make every effort to keep subjects' personal information confidential, there is a small, theoretical risk that an unauthorized person might see this information. All subjects will be advised that we are unable to guarantee total privacy at the time of providing informed consent.

Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/potential discomforts to subjects:

To better quantify the physical discomfort associated with POCUS in the postpartum period, we have performed the planned ultrasound protocol in a small number of patients admitted to our postpartum unit. The patients who have experienced the ultrasound protocol to this point have undergone both vaginal and cesarean births and have spanned a range of body mass indexes. Each patient was queried as to the comfort or discomfort associated with POCUS, and all patients responded that the studies caused little to no discomfort. None of the patients required any analgesia to tolerate the study, though we would plan to offer enrolled subjects any of the postpartum analgesics (e.g. acetaminophen, ibuprofen) prescribed to them prior to pursuing POCUS. While the required lab draws would presumably be associated with more discomfort, all blood draws will be completed in the same fashion in accordance with UCI protocols. Subjects will

be monitored in the postpartum unit for all study labs draws so that any pain reactions can be addressed in a timely manner.

We hope to further reduce the potential physical risks associated with furosemide use by excluding all patients with known contraindications to this medication such as confirmed allergy, prior adverse reaction, baseline hypokalemia, and baseline renal dysfunction.

Is the research partially or wholly funded by NIH (including NIH Institutes and Centers), or does the research involve identifiable sensitive information that require CoC protections?
No

Is there the prospect of a direct benefit anticipated for subjects?
Yes

Describe the potential benefits subjects may expect to receive from participation in this study:
Subjects with postpartum preeclampsia and evidence of volume overload may benefit from study participation by virtue of receiving diuretics as an adjunct to their standard antihypertensive therapy. This intervention has been proven to significantly decrease blood pressure within 2 hours of administration (Lopes Perdigao et al, 2021), which may translate to a decreased need for antihypertensive agents, shorter length of hospital stay, and a decreased likelihood of hospital readmission.

Specify the expected potential societal/scientific benefit(s) of this study:
The primary benefit for the greater obstetric community is that this research has the potential to clarify the mechanisms underlying preeclampsia recovery in the postpartum period. If the results are compelling, this study might also inform new strategies to optimize care of postpartum patients with preeclampsia. In our health care system, this could manifest as a reduction in the number of postpartum hospital admissions as well as the financial burden of these re-admissions. Beyond the clinical benefit, since we have proposed a pilot study, this research could lay the foundation for future resident, fellow, and attending projects, including randomized controlled trials.

Alternatives to Participation

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable (check all that apply):
Routine standard of care available

Specify the routine standard of care:
As stated earlier in this document, routine standard of care for preeclampsia in the postpartum period involves serial blood pressure measurement as frequently as every 15 minutes for values consistent with severe hypertension (> 160/110 mm Hg) and every 6 hours for values consistent with normotension or mild hypertension (< 160/110 mm Hg). Patients with severe hypertension are managed according to current inpatient protocols with intravenous antihypertensives. Patients with mild hypertension (140 – 159/90 – 109 mm Hg) are started on oral antihypertensives such as labetalol or nifedipine at the discretion of the managing physician. Patients are eligible for

discharge home beginning on postpartum 2 day if their blood pressure has been at goal (< 150/100 mm Hg) for at least 12 hours.

Participant Compensation

Will subjects be compensated?
No

Will subjects be reimbursed for out-of-pocket expenses?
Yes, though none are anticipated.

Describe any requirements for reimbursement (e.g., receipt):
Subjects would need to provide a copy of the associated receipt or itemized billing statement.

Participation Costs

Will subjects or their insurers be charged for study procedures?
The POCUS aspect of the study procedure will not be associated with any costs to subjects or their insurance providers, as this will be performed free-of-charge by study personnel. If diuretic therapy is indicated based on POCUS results, this will be charged to insurance companies who are already covering this treatment for postpartum patients with preeclampsia. Similarly, as obtaining comprehensive metabolic panels is part of the standard evaluation for preeclampsia, any comprehensive metabolic panels obtained as part of study participation will be charged to subjects' insurers. The one exception to this is BNP lab draws, which are not routinely part of standard preeclampsia evaluation or management. For this reason, we intend to pay for baseline and follow-up BNP levels with study funds.

Confidentiality of Research Data

Indicate how information and/or biospecimens (including signed consent forms) will be stored (check all that apply):

- Information will be maintained electronically. Information will be password protected and maintained in an encrypted format
- Information will be maintained in hard copy. Information will be stored in a locked area that is not accessible to non-study team members

Specify where the information will be maintained electronically:
Patient data will be securely maintained in both REDCap and the UCI research cyberinfrastructure center.

Specify where the information will be maintained in hard copy:
Paper consent forms will be stored in the Maternal-Fetal Medicine offices at Chapman Pavilion (3800 W. Chapman Avenue, Orange, CA 92868).

Will subject/patient identifiers be collected or retained?
Yes, during the data collection period subjects' names, medical record numbers, dates of birth, and telephone numbers will be retained to facilitate follow-up after hospital discharge. However, once the data collection period is complete and analysis begins, all data will be de-identified and subject identifiers will be removed from study databases.

Will any subject/patient identifiers be collected or retained for data analysis, recruitment, consenting and/or compensation (check all that apply)?

- All elements of dates (except year) for dates that are directly related to an individual: birth date, admission date, discharge date, death date, and all ages over 89
- Medical record numbers
- Telephone numbers

Will a code be used to link subject/patient identifiers with the information and/or biospecimens?
Yes, a unique subject identification code will be used. Subject identifiers will be kept separately from the study data. The code key will be destroyed at the earliest opportunity, consistent with the conduct of this research.

Will research data/biospecimens be transported or maintained on portable devices (e.g., laptop, smartphone, external hard drive, etc.)?
No, as above, all data will maintained through REDCap and the UCI resesarch cyberinfrastructure center.

Specify who will have access to subject/patient identifiable information/biospecimens as part of this protocol (check all that apply):
Authorized UCI personnel (such as the research team) and appropriate institutional officials: such as the Office of Human Research Protections (OHRP) Regulatory entities such as the Food and Drug Administration (FDA), the National Institutes of Health (NIH)

Specify whether subject/patient identifiers be disclosed in presentations and/or publications:
No, subject identifiers will not be disclosed in any forthcoming presentations or publications.

Specify how long all subject/patient identifiers will be retained. This includes identifiers stored in paper format, stored electronically as well as video recordings, audio recordings, photographs, etc.:
All subject identifiers will be retained through completion of the data collection phase, after which only deidentified information will be retained through the data analysis, presentation, and publication phases.

Indicate how long research information/biospecimens will be retained:
In accordance with UCOP policy, information will be retained for 10 years after the end of the calendar year in which the research is completed, unless otherwise specified in any future award agreements.

Will research information and/or biospecimens be shared?
No