Oral combined Hydrochlorothiazide/Lisinopril versus oral nifedipine for postpartum hypertension: A comparative effectiveness pilot randomized

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Oral combined Hydrochlorothiazide/Lisinopril versus oral nifedipine for postpartum hypertension: A comparative effectiveness pilot randomized controlled trial

Study protocol

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Background and significance:

Hypertensive disorders of pregnancy (HDP) complicate up to 10% of pregnancies and are a significant cause of maternal mortality and morbidity.[1] Hypertension may be present before or during pregnancy or in postpartum. Postpartum hypertension can be related to the persistence of gestational hypertension,preeclampsia, preexisting chronic hypertension, or it could develop de novo secondary to other causes. While most research efforts have mainly been focused on the antenatal management of hypertension for a maternal and fetal benefit, there is a paucity of studies evaluating the behavior of postpartum hypertension and the pharmacologic therapies during this period to optimize maternal safety and minimize hospital stay.

Postpartum hypertension results in increased medical costs due to prolonged hospitalization, the need for magnesium sulfate and antihypertensive drugs, and increased hospital readmission rates. People with hypertensive disorder of pregnancy are at increased risk for immediate postpartum complications, including hypertension-related complications (i.e., uncontrolled blood pressure, acute cardiovascular disease, acute cerebrovascular disease, acute renal insufficiency), and obstetric related postpartum complications (i.e., infection, hemorrhage, venous thromboembolism). [2] Hypertensive disorder of pregnancy, and chronic hypertension are a risk factor for stroke during the postpartum period, with the majority of stroke readmission after birth occurring in the first 10 days after discharge. [3] Despite the cure for preeclampsia being the delivery of the infant, maternal health implications persist well beyond the pregnancy. Preeclampsia is associated with maternal cardiovascular dysfunction and

long-term cardiovascular risk,[4-9] including a 2-fold risk of ischemic heart disease and stroke and a 4-fold risk of hypertension in later life.[7,8,10-12] The association between preeclampsia and future CVD persists, despite accounting for mutual risk factors, including age, obesity, and prepregnancy hypertension.[13] Cardiovascular disease is not only more common in people with preeclampsia, but it tends to occur earlier, with a higher fatality rate. [8]

For many asymptomatic women, antenatal care is their first adult engagement with the healthcare system. Consequently, pregnancy and the early postpartum provide an ideal window for risk screening and primary prevention of long-term cardiovascular health and future pregnancy outcomes.

The American College of Obstetricians and Gynecologists (ACOG) recommends close outpatient blood pressure monitoring in all women with preeclampsia 7-10 days (or sooner if the patient is symptomatic) after delivery as the standard of care. Blood pressure rises progressively over the first five postnatal days, peaking on days three to six after delivery.

Blood pressure medication during the postpartum period:

During the immediate hospital stay after delivery, antihypertensive medications are recommended after delivery if systolic BP remains persistently ≥150 mm Hg and/or if diastolic BP ≥ 100 mm Hg. [14] However, there are no clear guidelines on optimal blood pressure management in the postpartum period. Based on previous data, at least 60-70% of women diagnosed with preeclampsia before delivery will require BP medications at discharge.[15-17] [18]At three months postpartum, 39% of women still had hypertension

(defined as blood pressure ≥140/90), which decreased to 18% at two years postpartum. [17]

A case-control study has also found that readmitted patients with HDP were less likely to start antihypertensive medications during their initial hospitalization after controlling for age, race, and chronic hypertension. [19] Based on previous data during readmission for hypertension, more than 50% of patients will start hypertensive medications. [20]

Despite the widespread use of antihypertensive drugs in the postpartum period, there is limited evidence regarding the preferred antihypertensive agent in that period (Table1). Usually, the selection of the antihypertensive agent is based on clinical judgment, as there are no standardized management guidelines for specific antihypertensive agents or parameters for postpartum medication titration.[18]

Table 1: Randomized controlled studies evaluating medications for postpartum hypertension

Study/ Year	Population/ Total number of patients	Intervention	Control	Primary outcome	Results
Calcium channel blockers					
Barton[21]/ 1990	Severe preeclampsia N=32	Nifedipine (oral,10mg)	Placebo	MAP	Reduction in MAP with nifedipine between 18-24 hours postpartum (93.9 versus 100.2 mm Hg; p less than 0.05)

Vermillion [22]/1998	Severe BP (170/105) N=50	Nifedipine (oral,10mg)	Labetalol 20mg IV	Time to achieve therapeutic goal (<160/100)	Time to achieve BP goal shorter with nifedipine (25 ± 13.6 min vs. 43.6 ±25.4 min; P =.002).
Arias-Hernandez [23]/2020	Postpartum preeclampsia with severe features N=42	Diltiazem (oral,60mg TID)	Nifedipine (oral,10mg TID)	SBP, DBP, MAP	At 6 hours, lower SBP (133.4±10.2) vs. 147.9 ±9.7,p<0.001) and DBP (78.5±7.7) vs. 90.6 ±5.5, p<0.001) with Diltiazem
Beta-blocker					
Fidler[24]/ 1982	Postpartum HTN (DBP 95-105) N=80	Timolol (oral)	Methyldopa (oral)	SBP, DBP	Lower SBP with Timolol (difference 5.1mmHg, p<0.05)
Mabie[25]/ 1987	Severe Postpartum HTN (DBP>110) N=60	Labetalol (IV 20-80mg)	Hydralazine (IV 5mg)	MAP	Improved in the control group (difference 5.1mmHg, p<0.02)
Sharma[26]/ 2017	Postpartum HTN (>150/100) N=50	Labetalol (oral 200mg BID)	Nifedipine (30mg daily)	Time to BP control	No difference (37.6 hours versus 38.2 hours, p = 0.51)
Diuretics					
Matthews[27]/1997	Preeclampsia N=19	Furosemide (oral, 40mg, 7 days)	Placebo	Mean BP, Max BP	No difference
Ascarelli[28] /2005	Preeclampsia N=264	Furosemide (oral, 20mg, 5 days) +	Placebo	SBP	No benefit for patients with mild

		Oral potassium supplementation			preeclampsia (n = 169) or superimposed preeclampsia (n = 25). Patients with severe preeclampsia had lower SBP (142±13 mm Hg vs 153±19 mmHg, P < .004), and required less antihypertensive therapy during hospitalization (14% vs 26%, P = .371)
Venna[29]/ 2017	Postpartum HTN (>150/100) N=108	Furosemide (oral, 20mg, 3 days) + Nifedipine (10mg TID)	Nifedipine (10mg TID)	SBP,DBP, MBP, need for additional HTN drugs	No difference in BP. Requirement of additional antihypertensive higher in in Nifedipine alone group (26.0% vs. 8.0%, p = 0.017)
Viteri[30]/ 2018	Preeclampsia N=118	Torsemide (20 mg, 5 days)	Placebo	BP>150/100 by day 5 or discharge	No difference
Perdigao[31]/ 2021	Gestational hypertension/preeclampsia	Furosemide (oral, 20mg, 5 days)	Placebo	persistent hypertension 7 days postpartum	60% reduction in the prevalence

	N= 384			(at least 2 consecutive BP readings over 48 hours of SBP ≥140 and DBP ≥90)	of persistent hypertension at 7 days (adjusted relative risk, 0.40 [95% CI, 0.20–0.81])
ACE inhibitors					
Ormesher [32]/2020	Preterm preeclampsia N= 60	Enalapril 5 mg daily for 1 week> 10 mg for 2 weeks then 20 mg maintenance dose for 6 month	Placebo	reduction in total vascular resistance from baseline to 6 months	No difference
Alpha agonists					
Carlos Noronha Neto[33]/ 2017	Severe HTN (≥180/110) N=90	Clonidine (oral, 0.1mg)	Captopril (oral, 25mg)	frequency of very high BP episodes (≥180/110) while in the obstetric ICU	No difference
Hydralazine					
Griffis[34]/ 1989	Gestational HTN N=26	Hydralazine	Methyldopa	MAP	No difference
Vigil-De Gracia[35]/ 2007	Severe HTN (≥160/110) N=82	Hydralazine (IV, 5mg)	Labetalol (IV, 20mg)	Persistent severe BP	No difference

SBP; systolic blood pressure, DBP; diastolic blood pressure, MAP; mean arterial pressure

Angiotensin-converting enzyme inhibitors (ACE inhibitors) in the postpartum period.

A review of the available observational literature concluded that the following drugs have minimal milk to maternal plasma ratios to make breastfeeding acceptable: methyldopa, beta-blockers with high protein binding, angiotensin-converting enzyme inhibitors, and some dihydropyridine calcium channel blockers.[36] These drugs are used in the postpartum period, but the most common hypertensive treatment for antepartum and postpartum hypertension is Nifedipine and Labetalol.[37] ACE inhibitors are not used during pregnancy due to the higher risk for teratogenic effects but may be used in the postpartum period. ACE inhibitors are recommended for those with pregestational diabetes mellitus or cardiomyopathy and are the 1st drug of choice by the National Institute for Health and Care Excellence (United Kingdom) for postpartum hypertension.[37-39]

ACE inhibitors play an important role in controlling blood pressure outside of pregnancy. There is extensive evidence to support their cardioprotective effects. The HOPE (Heart Outcomes Prevention Evaluation) study, during which participants at high risk of cardiovascular disease were randomized to ramipril or placebo, was stopped prematurely due to the 22% reduction in myocardial infarction, cerebrovascular accident, or death from cardiovascular disease.[40]

ACE inhibitors may be used in the postpartum period without effect on breastfeeding, but the evidence on the effect of ACE inhibitors on postpartum hypertension treatment is limited.[32,38,41-44]

Normal pregnancy has been identified as a state of relative resistance to the pressor effects of Angiotensin II (Ang II).[45] In contrast, pregnant people with new-onset hypertension demonstrate increased sensitivity to the pressor effects of Ang II, even before the onset of hypertension.[45,46] Increased sensitivity to angiotensin II observed during pregnancy in women with hypertensive pregnancy was also present postpartum.[47] There is only one randomized study comparing captopril and clonidine for severe range blood pressure in the postpartum period. The above study concluded that both clonidine and captopril were safe and effective treatments for severe postpartum hypertension.[33] There are no studies to date comparing ACE inhibitors to other oral medications to control non-severe blood pressure in the postpartum period.

A recent randomized, double-blind placebo-controlled trial evaluated six months' treatment with enalapril to improve postnatal cardiovascular function in women with preterm preeclampsia. The primary clinical outcome was reduction in total vascular resistance (TVR) from baseline to 6 months post randomization following treatment with enalapril, compared with placebo. There was no difference in the TVR between groups at 6 months postpartum. Similarly, there was no difference in systolic function (measured by left ventricular ejection fraction/global longitudinal strain). However, individuals who were treated with enalaprilhad a significantly better diastolic function and improved LV remodeling, compared with placebo at 6 months than those treated with placebo. [32]

Our experience with ACE inhibitors in the postpartum period has been favorable, but given the lack of data regarding use of ACE inhibitors in the postpartum period, it may not be an adequate drug for first-line treatment for persistent postpartum hypertension.

Diuretic use in the postpartum:

In individuals with preeclampsia, persistent hypertension and edema result in part from the mobilization of up to 8 liters of fluid and sodium from the extravascular to intravascular space. The increased urinary sodium excretion on days 3-5 postpartum likely results from higher atrial natriuretic peptide concentrations in plasma and activation of the renin-angiotensin-aldosterone system. Adding diuretics for postpartum hypertension has been associated with better blood pressure control in some of the studies.[28,29]

Rationale for a Clinical Trial and Hypothesis

- CVD is the leading cause for mortality worldwide.
- Primary prevention is more effective than treating CVD.
- Pregnancy is often the 1st adult engagement with the healthcare system.
- Preeclampsia is a risk factor for long term CVD, even after controlling for mutual risk factors.
- CVD is the leading cause for pregnancy related mortality.
- There is no good data regarding the optimal medications to control blood pressure after delivery.
- ACE inhibitors play an important role in controlling blood pressure outside of pregnancy and there is extensive evidence to support their cardioprotective effects.
- The optimal use of diuretics in the postpartum in patients with preeclampsia, require further study and clarification to augment current management schemes.

Hypothesis: We hypothesize that in postpartum women with hypertensive disorders, oral combined Hydrochlorothiazide/Lisinopril will reduce postpartum hypertension at 7 days after delivery compared to usual care with calcium channel blockers.

PICO question:

Population: Puerperal women with hypertension within the first 72 hours after delivery.

Intervention: Hctz/Lisinopril for postpartum management of hypertension

Comparison: Extended release nifedipine

Outcome: Stage 2 hypertension at day 7-10 after delivery (defined as SBP ≥ 140 and/or DBP ≥ 90 mmHg) or admission to the hospital for blood pressure control prior to day 10.

Inclusion Criteria

- Postpartum women at ≥ 18 years of age
- Postpartum diagnosis of persistent hypertension (2 measurements of Systolic BP ≥150 and/or diastolic BP ≥ 100 or systolic BP ≥140 and/or diastolic BP ≥ 90 for people with diabetes) requiring an oral medication based on the ACOG criteria or
- Hypertensive disorder of pregnancy diagnosed antepartum or intrapartum requiring blood pressure medication in the postpartum
- Chronic hypertension requiring blood pressure medication postpartum

Exclusion Criteria

- Urine output < 30 cc/h prior to screening for eligibility

- Creatinine > 1.4 during current admission
- End-stage renal disease
- Hypersensitivity to ACE inhibitors or sulfa drugs
- Idiopathic/hereditary angioedema
- Hyperkalemia (serum potassium >5 mEq/L) during current admission
- Pulmonary edema

Randomization:

- Randomization will be achieved by computer-generated random sequences that will be created by a non-clinical member of the research team. A permuted block randomization with a random fashion will be used to prevent imbalances between groups.
- Randomization will be stratified according to:
    1. Primary diagnosis: chronic hypertension or newly diagnosed preeclampsia
    2. Recruiting site

Setting:

Recruitment will occur on the Labor and Delivery ward and postpartum ward at:

- Memorial Hermann Hospital-Sowthwest.
- Lyndon B. Johnson Hospital
- Memorial Hermann Hospital-Texas Medical Center.

Recruitment

- The research staff/MFM physician will approach individuals that meet the inclusion and exclusion criteria during their hospital stay before discharge.

- The research stuff will Introduce Babyscripts as a health system's mobile app and sign the patients up for Babyscripts.
- After adding the patient to the system, the patient will receive an email and a text message with a personal passcode to complete registration.
- The patient will download the Babyscripts myJourney app on her smartphone and enter the personal passcode under "New User" where it indicates. From there, the patient will be prompted to fill in some additional information to complete registration.
- Once the patient completes registration, we will provide her with a BP monitor so you can start taking readings through the app.
- The patients will be instructed to monitor their BP twice daily, in the morning and the evening.
- Of Note, Babyscripts sends daily SMS reminders, twice a day, to remind patients to check their blood pressure.

Intervention and procedures

- Participants will be randomized to Hctz/Lisinopril (brand name: *Zestoretic)* or extended release Nifedipine. Group 1 will be composed of women allocated to Hctz/Lisinopril treatment. Group 2 will be composed of women allocated to extended release Nifedipine treatment.
- Hctz/Lisinopril and extended release Nifedipine will be administrated orally in the morning for both groups.
- The allocated study medication will be incrementally increased to achieve blood pressure control according to the threshold listed below (Table 2).

- If maximum dose of one medication will be reached without blood pressure control, oral labetalol will be added at the lowest dose increasing as needed.
- Hctz/Lisinopril will be started at 10mg/12.5 daily
- Extended release Nifedipine will be starts at 30mg daily
- The use of concomitant intravenous antihypertensive medication (i.e Hydralazine, labetalol) for severe hypertension as well as the use of magnesium sulfate for seizure prophylaxis will be left to the discretion of the treating medical team
- Following hospital discharge, twice a day (8am and 7pm), patients will receive SMS and push notifications to remind them to take their BP through the Babyscript app. If patients have three missed readings in a row, they will receive a SMS and push notification.
- information will be collected from the medical record including medical and pregnancy history, lab results, delivery and postpartum information.

Table 2: Dose adjustment plan

	Initial dose	Dosing adjustment	Maximum dose/day
Extended release **Nifedipine**	30mg/ day	Increase by 30mg/day	90mg/day
Lisinopril/Hydrochlorothiazide	10mg/ 12.5mg/day	Increase by 10mg lisinopril/day to 20mg/12.5 mg	20/25/day

		Next increase will be with the HCTZ to 20mg/25	

Thresholds for action based on raised blood pressure in the postpartum period: The following recommendations for blood pressure treatment in the postpartum period are based on the ACOG and NICE guidelines[38]

- During hospital stay:
    - SBP≥160 or DBP≥110, repeat BP in 15 minutes
    - If persistent, give intravenous medication to lower blood pressure and increase oral medication the next morning
    - SBP ≥150 or DBP≥100, repeat BP in 4 hours
    - If persistent, increase oral medication the next morning
- After discharge from the hospital
    - SBP≥160 or DBP≥110, repeat BP in 15 minutes
    - If persistent, refer for evaluation in the clinic or the emergency department
    - SBP≥150 or DBP≥100 in BP monitoring at home or in postpartum clinic, increase oral medication the next morning

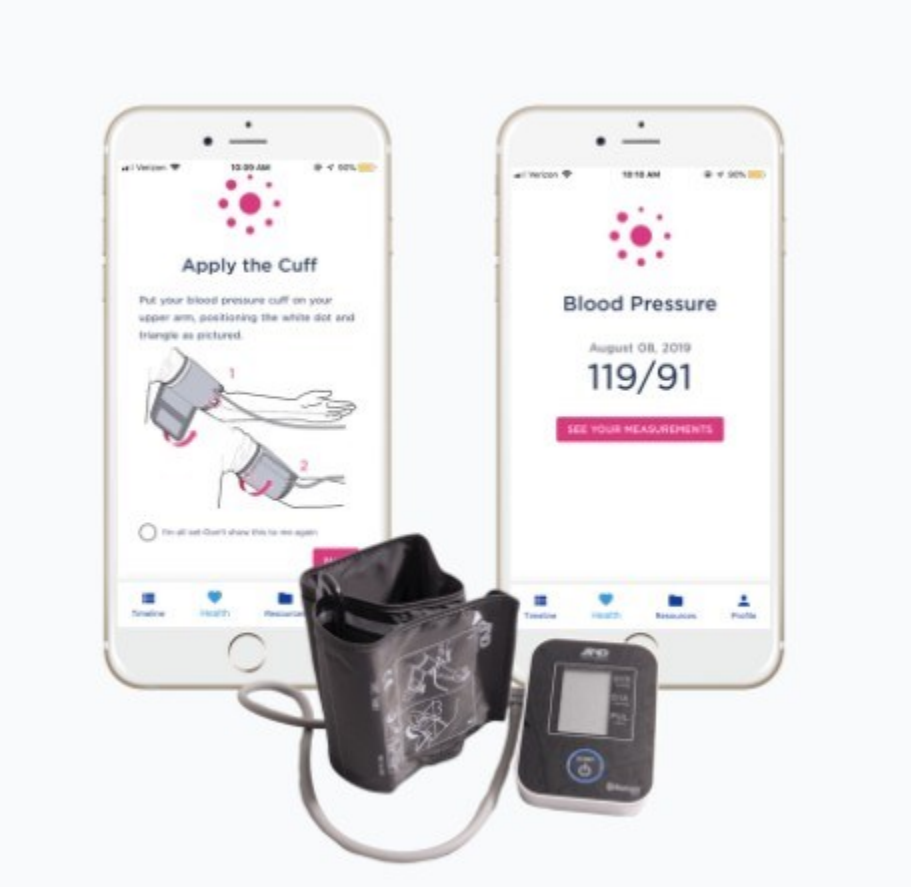
Outcome measures:

- All patients will receive a Bluetooth BP cuff at during the hospital course.
- The BP cuff will be connected via Bluetooth to a Babyscripts application and available for the research team to review (Figure 1).

- The Babyscripts app is a resource for all UT Physicians obstetrical patients during their pregnancy and postpartum.
- The participants will be instructed to measure their BP twice daily until their clinic appointment.
- Following their postpartum clinic appointment the participants will be instructed to measure their BP once daily.

- All patients will be followed in the clinic 7-10 days after delivery and 6 weeks postpartum as recommended by the ACOG guidelines
- Patients will be contacted 3 month, 6 month and 1 year after delivery by telephone for information regarding blood pressure control, medication use.

Figure:



Primary outcome:

Stage 2 hypertension at day 7-10 after delivery (defined as SBP ≥ 140 and/or DBP ≥ 90 mmHg) or admission to the hospital for blood pressure control prior to day 10.

Primary outcome will be calculated as the average BP reading for day 7-10 after delivery.

Secondary outcomes:

- Occurrence of severe postpartum hypertension (SBP≥160 and/or DBP≥110 mmHg on 2 occasions, 15 minutes apart)
- Receipt of additional antihypertensive during admission, at 7-10 postpartum, and at 6 weeks postpartum.

- Postpartum length of stay
- Postpartum readmission
- Time from delivery to BP control (i.e time from delivery to last BP <150/100).
- Incidence of persistent postpartum hypertension 6 weeks postpartum (SBP ≥ 140 and/or DBP ≥ 90 mmHg).
- Proteinuria at 7-10 days, and 6 weeks postpartum (measured by urine protein creatinine ratio).
- Labs abnormality including hyperkalemia or creatinine increase at 7-10 day visit and 6 weeks postpartum.
- Compliance with medications at postpartum visit at 7-10 days after delivery and 6 weeks postpartum. The patient will be asked to bring their medication bottle with them and the compliance will be measured by counting pills at each postpartum visit.
- Blood pressure control at 3 month, 6 month, 9 month, 1 year after delivery and need for BP medications.
- % of patients receiving primary care with BP measurement at 1 year.
- Postpartum complications captured as Severe composite maternal morbidity:
    - Need for ICU admission
    - HELLP
    - Eclampsia
    - Stroke
    - Renal failure
    - Pulmonary edema

  - Cardiomyopathy
  - Maternal death
- Blood pressure control at 3 month, 6 month, 9 month, 1 year after delivery and need for BP medications
- % of patients receiving primary care with BP measurement at 1 year

Sample size:

Due to lack of information regarding the prevalence of persistent hypertension 7 days after delivery, and the limited information regarding the use of ACE inhibitors in the postpartum period, this will be a pilot study that will include 70 patients. That sample size will allow us to gather information regarding feasibility, compliance, rate of the primary outcome, dosing of medications, and side effects.

Feasibility:

Based on data from our center, in the 3 participating centers there are 6,574 deliveries per year. With 10% rate of preeclampsia, 657 people per year will be eligible to participate in this trial. Assuming 30-50% of patients will decline to participate, we will expect to recruit 70 patients in 6-9 month.

Blinding:

- We will not be able to blind the treating physician or patient to the study medication due to different dose adjustment, side effects, etc
- However, the research person who would review the 7-10 day BP measurements will be blinded to treatment assignment

Procedures for safety monitoring:

- A review of the available observational literature concluded that extended release nifedipine and ACEI have minimal milk to maternal plasma ratios to make breastfeeding acceptable.
- Additionally Severe BP (SBP≥160/DBP ≥110) will be reported by the babyscript app to the physician via text and email, and the team will contact the patient for further management

Statistical tests:

- An intent-to-treat analysis will be conducted. Outcomes will be evaluated using the independent t-test for continuous variables and the x^2 or fisher's exact test for categorical variables as appropriate. Mann-Whitney U test will be used for non-parametric comparisons. We will report RR and 95% confidence intervals. Secondary outcome measures will be compared.
- We will conduct a Bayesian analysis to calculate the probability of treatment benefit or hram. The probability of at least 20% reduction in the rate of the primary outcome will be considered clinically significant. we conservatively set a neutral prior probability centered at a relative risk (RR) of 1.0 (*i.e.*, a priori no effect on the outcome) and a 95% credible interval of 0.25 – 4.0.

Ancillary Studies

1. **Medication adherence survey**: Medication non- adherence is an important public health issue that clinicians encounter. Approximately 78% of e-prescriptions are

actually filled; only 72% of new prescriptions are filled.[48] Non-compliance is most common among new prescriptions for chronic conditions including hypertension(31.4%). Adherence to medications can be affected by a variety of factors in patients with hypertension; the perception that drugs are only needed when blood pressure levels are high, concerns regarding adverse effects, and lack of self-confidence in their self-treatment. Medications are commonly used in pregnancy and postpartum, with at least 81.2-96.9% of women using at least one medication, either prescribed or over-the-counter.[49,50] The attitudes regarding drug use in pregnancy and obtaining drug information play an essential role in medication adherence[51]. The MMAS-8 validated survey (attached as Figure 1) will be given to women to complete their routine postpartum care during their clinic visit if they meet study criteria and agree to the study. This survey will be supplemented with other questions about demographics and challenges with prescription error and pick-up problems. It takes less than 10 minutes to complete. The answers will not be available to the managing health care provider but will be kept in the locked research office until after the delivery of the subject. Based on the survey scores, the subject will be divided into groups based on high, medium and low adherence. Outcomes between groups will be compared.

2. Social determinants of health (SDH) Survey (SDH)- while our approach to clinical care is rooted in biology, an increasingly interdisciplinary approach is being employed that acknowledges SDH, i.e., the social and structural aspects of a 'patient's life that can influence health. Social determinants of health (SDH) include but are not limited to basic resources, educational opportunities and economic stability, access to health care,

community resources, literacy, socioeconomics, and safety.[52] By understanding SDH, interventions can be pursued that can improve individual and population health. For patients living with hypertension, there is a correlation between social determinants of health and blood pressure control. SDH also impacts many obstetrical conditions. [53] Using this broader context to understand 'patients' health care decision-making and health literacy facilitates the intersections of social identity and their associated patterns of structural oppression and fosters a creative approach to overcoming potential barriers. The PRAPARE Assessment (The Protocol for Responding to and Assessing' Patients' Assets, Risks, and Experiences) is an established tool to assess SDH briefly. Core measures of this tool include race, ethnicity, education, employment, insurance, income, material security, transportation, social integration and support, stress and migrant, veteran and housing status. It will provide insight by which we can understand correlations between SDH and health care outcomes in our population as a springboard to improving both the outcomes and the pathways leading to them. The brevity of questions covering numerous social domains can help target particular social features that may be correlated with blood pressure control as well as target resource referrals and utilization, thereby translating into actionable items.

Ethical considerations

Informed consent

All study candidates will be given a full explanation of study, allowed to read the informed consent, and be provided the opportunity to ask any questions. Once all questions have been answered and the investigator is assured that the individual

understands the requirements of the study, the subject will be signing an informed consent. The investigator shall provide a copy of the informed consent.

Institutional review board

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

Subject confidentially

Each study's subject anonymity will be maintained throughout the study. Before collecting the data, a unique study number will be assigned to each case, thus de-identifying the individual subject. There will be a log of the study subject to the assigned study number in the study site.

Research assistants are in compliance with required CITI training. When the results of this research study are reported in medical journals or at scientific meetings, the subjects who take part will not be named or identified. The Federal Privacy Act protects the confidentiality of medical records and any private health information collected. Access to personal data will be limited to the investigators only. However, these individuals are required to keep all information confidential.

Data handling and record-keeping

Access to source documents:

Research personal will perform data collection manually from patient charts at the different sites. Please refer to the attached data collection sheet for detail on variables to be collected. Data will be collected from randomization until one year postpartum.

Records retention: Data will be digitally encrypted and stored in the UTHealth Redcap system. After the study, the principal investigator will retain copies of the approved protocol and all other supporting documentation related to the project. De-identified patient information may be used for future research projects.

Quality control Assurance: the principal investigator and co-investigators will go through all the files to assure that data is reliable and complete. The verification will be by self-assessment.

Figure 1: Morisky Medication Adherence Questions (MMAS-8).

These are questions about your medication adherence. Please circle or select one option.

1. Do you sometimes forget to take your medicine? No Yes

2. People sometimes miss taking their medicines No Yes

for reasons other than forgetting. Were there any days when you did not take your medicine?

3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it? No Yes

4. When you travel or leave home, do you sometimes forget to bring along your medicine? No Yes

5. Did you take all your medicines yesterday? No Yes

6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine? No Yes

7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? No Yes

8. How often do you have difficulty remembering to

take all your blood pressure medication?

_____A. Never/rarely

_____B. Once in a while

_____C. Sometimes

_____D. Usually

_____E. All the time

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