Torsemide for the Prevention of Persistent Postpartum Hypertension in Preeclamptic Women: A Randomized, Placebo-Control trial

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Torsemide for the Prevention of Persistent Postpartum Hypertension in Preeclamptic Women: A Randomized, Placebo-Control trial

STUDY PROTOCOL

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TROPHY TRIAL
(ToRsemide for pOstPartum HYpertension)

BACKGROUND AND SIGNIFICANCE

Pregnancy related hypertensive disorders complicate up to 10% of pregnancies worldwide. Indeed, the incidence of preeclampsia has increased 15% in the United States over the past two decades[1]. While most research efforts have mostly been focused on the antenatal management of hypertension for 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[2–7]. Indeed, **persistent postpartum hypertension results in increased medical costs due to prolonged hospitalization, need for magnesium sulfate and antihypertensive drugs, as well as increased hospital readmission rates**. In the long term, women with persistent hypertension are at increased **risk for developing cardiovascular disease and kidney failure later in life**[8].

The exact incidence of postpartum hypertension is difficult to ascertain since most women will not have their BP checked until their 6-week postpartum visit[2]. It is generally accepted that the reported prevalence of new onset hypertension-preeclampsia in the postpartum period ranges from 0.3-27.5%[2]. In 2010, a large population-based study reported that 0.3% of all postpartum visits to the emergency departments were due to hypertension or preeclampsia[7]. These conditions are either secondary to persistent hypertension or exacerbation of gestational hypertension, preeclampsia, chronic hypertension or because of a new onset disease[2].

Pathogenesis of Postpartum Hypertension

In women with preeclampsia, BP usually decreases within 48 hours following delivery, but increases again 3-6 days postpartum. In contrast, development of *de novo* hypertension in the postpartum period, elevated BPs appear for the first time after delivery through 6-weeks postpartum. One study demonstrated that 44% of eclampsia cases occurred in the first 48 hours[9], and a recent large retrospective study found that 63% of patients readmitted with postpartum hypertension had no antecedent diagnosis of pregnancy-related hypertensive disorders. Regardless of the antepartum diagnosis of preeclampsia, the authors concluded that the risk of eclampsia was highest within 7 days after delivery[10]. **This prompted the American College of Obstetricians and Gynecologists (ACOG) to recommend close outpatient blood pressure monitoring in all women with preeclampsia 7-10 days (or sooner if the patient is symptomatic) after delivery as standard of care**[11].

It is believed that, in women with preeclampsia prior to delivery, persistent hypertension and edema result from mobilization from the extravascular to the intravascular space of 6-8 liters of total body water and sodium (950 mEq) accumulated during pregnancy[6]. The increased urinary sodium excretion was observed on days 3-5 postpartum, likely as a result of increase in atrial natriuretic peptide (ANP) and activation of the renin-angiotensin-aldosterone system[12]. However, preeclampsia and eclampsia can develop up to 4 weeks postpartum. Compared to women with preeclampsia, fewer women with gestational hypertension appear to have postpartum hypertension. Also, the duration of this hypertension appeared to be shorter (mean ± SD of 6 days, SD 5.5 days) that in women with preeclampsia[13].

Role of Loop Diuretics in Postpartum Hypertension

Recent studies have proposed the use of loop diuretics to steepen the slope of excess extravascular fluid characteristic of women with preeclampsia in an effort to decrease hypertensive complications in the postpartum period[14,15] (Table 1). As the most effective diuretic class, loop diuretics inhibit the Na^+-K^+-$2CL^-$ symporter at the thick ascending limb of the loop of Henle. This symporter captures free energy in the Na^+ electrochemical gradient established by the basolateral Na^+ pump and provides for an uphill transport of K^+ and Cl^+ into the cell. K^+ channels in the luminal membrane provide a conductive pathway for K^+ recycling. Hyperpolarization of the luminal and depolarization of the basolateral membranes result in a transepithelial potential difference of 10 mV (lumen positive relative to the interstitial space), due to the presence of Cl^- ions. This lumen positive potential repels cations (Na^+, Ca^{2+} and Mg^{2+}) and provides an important driving force for the paracellular flux of these cations into the interstitial space. Loop diuretics block the function of the luminal symporter bringing salt transport in this segment to a virtual standstill. The same remains true for other cations. Increased luminal concentrations of Na^+ further depolarize de luminal membrane and therefore enhance the negative voltage gradient, which facilitates K^+ excretion. Finally, activation of the renin-angiotensin-aldosterone axis also contributes to K^+ and H^+ excretion. Notably, this phenomenon is less pronounced with Torsemide, which antagonizes the aldosterone receptor[16]. Table 2 depicts the pharmacokinetic characteristics of loop diuretics available in the US. Pharmacodynamic properties are depicted in Table 3.

Table 1. Studies on Loop Diuretics for the Prevention of Postpartum Hypertension

Study	Inclusion Criteria	Intervention	Control	Primary Outcome
Mathews 1997 RCT (n=19)	Postpartum women with severe preeclampsia before delivery	Furosemide: 40 mg/d x 7d	Placebo	Fall in mean MAP (NS) Need for antihypertensive (NS) Mean Length of Stay (NS)
Ascarelli 2005 RCT (n=264)	Postpartum women with preeclampsia or superimposed preeclampsia before delivery	Furosemide: 20 mg/d x 5d KCl: 20 mEq/d x 5d	N/A	Mean postpartum BP 142±13 vs 153±19 mmHg P<0.004 for severe disease only Antihypertensive at D/C 6% vs 26% P = 0.045 for severe disease only
Tuuli 2015 RCT (n=248)	Postpartum women with gestational hypertension, preeclampsia and severe preeclampsia before delivery	Furosemide: 40 mg/d x 6d KCl: 20 mEq/d x 6d	Placebo	CMM 0-6 wks postpartum - Antihypertensive at D/C - Readmission for hypertension - End organ damage Currently recruiting
Figueira 2015 RCT (n=120)	Postpartum women with preeclampsia before delivery	Furosemide: 20 mg/d x 5d	Placebo	Mean postpartum BP (from 24 h to 15 days after delivery) Enrollment completed

Abbreviations: RCT = randomized controlled trial, MAP = mean arterial pressure, NS = not significant, BP = blood pressure, D/C = discharge, CMM = composite maternal morbidity

Table 2. Pharmacokinetic Properties of Loop Diuretics

Property	Furosemide	Bumetanide	Torsemide
Relative potency	1	40	3
Affected by food	Yes	Yes	No
Bioavailability (%)	10-100% (avg. 50)	80-100	80-100
Onset of action (min)	30-60	30-60	30-60
Metabolism	65% renal	62% renal	80% hepatic
Half-life (h)	1.5-2	1	3-4
Dosing (mg)	20-80 BID-TID	0.5-2 QD-BID	10-20 QD
Cost (US $)/100 tab	40 mg (100): $16.8	1 mg (100): $87.3	10 mg (100): $70.3

Abbreviations: QD = daily, BID = twice daily, TID = three times a day

Table 3. Pharmacodynamic Properties of Loop Diuretics

Property	Furosemide	Bumetanide	Torsemide
Lactation	Excreted (pregnancy category C)	No data (pregnancy category C)	No data **(pregnancy category B)**
Effect on RAA system	None	None	Inhibits
Cardiac effects	None	None	Improved LVED and LVES volumes, ↓ BNP and cardiac remodeling
Rebound Na retention*	↑↑↑	↑↑↑	None
Potassium loss	↑↑↑	↑↑↑	↑
Magnesium loss	↑↑↑	↑↑↑	↑
Calcium loss	↑↑	↑↑	↑
Quality of Life**	↓↓↓	↓↓↓	↓

* Suboptimal dosing (i.e. once a day) of furosemide results in rebound Na+ retention, decreasing diuretic effect.
** Torsemide is associated with less urgency and sensation of incomplete voiding than Furosemide or Bumetanide.
Abbreviations: RAA = renin-angiotensin-aldosterone system, LVED = left ventricular end-diastolic, LVES = left ventricular end-systolic, BNP = brain natriuretic peptide

Although diuretics are generally considered as second-line agents for the treatment of hypertension in pregnancy[11], is not known whether or not antihypertensive or diuretic therapy should be routinely instituted postpartum in women with antenatal preeclampsia in order to prevent postpartum hypertension[6]. An observational study of 67 women with preeclampsia found that 50% of women had a blood pressure greater than 150/100 mmHg on day 5 postpartum[17]. In a small randomized clinical trial (N = 19), postpartum women with preeclampsia and severe features before delivery received Furosemide 40 mg daily for 7 days

and were compared against placebo. No differences were noted in the mean and maximum blood pressure, need for antihypertensive treatment and mean length of hospital stay[14]. Conversely, in the no treatment arm of a larger randomized clinical trial (N = 264) comparing Furosemide 20 mg daily for 5 days with no intervention, 26% of women with preeclampsia were observed to require antihypertensive therapy at the time of hospital discharge (versus 6% in the Furosemide group)[15]. Notably, all these studies dosed Furosemide once daily.

Rationale for a Clinical Trial and Hypothesis

The evidence on the role of loop diuretics for the prevention of persistent postpartum hypertension is promising but limited. **ACOG recognizes that the optimal use of diuretics in the puerperium** in patients with preeclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome **requires further study and clarification** to augment current management schemes[11]**. Experience with Furosemide in the postpartum period has been favorable, but given its low potency, unpredictable bioavailability and suboptimal dosing with potential for rebound sodium retention, it may not be an adequate drug for first-line prophylaxis for persistent postpartum hypertension.**

There is no data available on the use of Torsemide in the puerperium. Growing evidence suggests the superior effect and safety profile of Torsemide when compared to Furosemide and Bumetanide in the management of edematous states, particularly given its higher potency, cardioprotective effects and more predictable bioavailability[18].

We **hypothesize** that in postpartum women with preeclampsia prior to or immediately after delivery, oral Torsemide (20 mg daily for 5 days) will reduce the rate of persistent postpartum hypertension requiring new or increased antihypertensive medications.

RESEARCH DESIGN & METHODS

Population

Puerperal women within the first 24 hours after delivery.

Primary Outcome

Persistent postpartum hypertension requiring new or increased doses of antihypertensive medications **at the time of hospital discharge** (SBP ≥ 150 and/or DBP ≥ 100 mmHg, on 2 separate occasions, at least 4 hours apart).

Secondary Outcomes

- Occurrence of severe postpartum hypertension (SBP≥160 and/or DBP≥110 mmHg on 2 occasions, 15 minutes apart)
- Need for postpartum readmission
- Length of hospital stay after delivery
- Weight change (from randomization to discharge)

- Changes in lower-extremity edema (from randomization to discharge)
- Incidence of persistent postpartum hypertension 7-10 days after delivery and 6 weeks postpartum (SBP ≥ 140 and/or DBP ≥ 90 mmHg)
- Side effects of therapy:
    - Hypokalemia
    - Failure to establish lactation
- Severe composite maternal morbidity:
    - Need for ICU admission
    - HELLP
    - Eclampsia
    - Stroke
    - Renal failure
    - Pulmonary edema
    - Cardiomyopathy
    - Maternal death

Ancillary Studies

It is not known whether Torsemide is excreted in breast milk. Prior to hospital discharge, we plan to collect a small sample of breast milk (3.5 mL) to measure the concentration of this medication in the breast milk, and 10 mL of maternal blood for serologic measurement of Torsemide concentrations as well as electrolyte profile.

Study Design

Randomized, double-masked, placebo-controlled trial.

Inclusion Criteria

- Postpartum women at ≥ 18 years of age
- Antepartum/intrapartum or within 24 hours postpartum diagnosis of either:
    - Preeclampsia
    - Preeclampsia with severe features
    - Preeclampsia superimposed to chronic hypertension

Exclusion Criteria

- Chronic hypertension without superimposed preeclampsia
- Gestational hypertension
- Urine output < 30 cc/h at time of randomization
- Heart failure or pulmonary edema
- Hypersensitivity to Torsemide or sulfonylureas
- Hypokalemia (serum potassium < 3 mEq/L)
- Preexisting diuretic use within 24 hours prior to randomization

Recruitment

Recruitment will occur on the Labor and Delivery ward at Memorial Hermann Hospital-Texas Medical Center.

Randomization

Central randomization will be conducted by Investigational Drug Service (IDS) pharmacy at Memorial Hermann Hospital-Texas Medical Center. Only the IDS pharmacy and study statistician will know the sequence of randomization. The subject will be randomized either to oral Torsemide 20 mg daily for 5 days or oral placebo daily for 5 days. If the patient is discharged before postpartum day 5, she will be given the study medication to take at home and complete 5 days.

Interventions and Procedures

Written informed consent will be obtained from participating women in the hospital setting only. Permuted block randomization with a random fashion will be used to prevent imbalances between groups. Study medications will be placed in sequentially numbered sealed opaque envelopes. Each envelope will contain a package containing either Torsemide tablets 20 mg or placebo tablets. An investigator who will administer the drugs will open these envelopes. Torsemide and placebo tablets will be identical. Both provider and participant will be blinded regarding the treatment administered. Women randomized to Torsemide will receive the medication once daily starting within 24 hours after delivery. Torsemide will be continued daily for a total of 5 days. The administration of placebo will follow the same protocol. Potassium supplementation will not be required since normally Torsemide is not associated with a significant degree of hypokalemia.

Blood pressure measurements for the primary outcome will be performed using a single pre-specified sphingomanometer at 3 time points: at randomization and at day 5 (or at discharge, whichever occurs first). If the BP on day 5 (or when patient is discharged) is between 150/100 mmHg and 170/110 mmHg, a second BP will be obtained within 4 hours (unless BP at any time after delivery was ≥ 150/100, in which case the subject will be considered a positive outcome). If BP is ≥ 170/110 mmHg, a new BP will be taken within 15 minutes. If persistent, the patient will be considered to have severe hypertension and will be managed as per unit protocol. In this case, the subject will also be considered as a positive outcome. If the criteria for persistent postpartum hypertension are met, the choice of antihypertensive medication, route and dosage will be left to the discretion of the treating physician.

Blood pressure measurements for secondary outcomes will be performed as per standard of care in the outpatient setting at 7-10 days after delivery (or pre-specified sphingomanometer if patient remains hospitalized) and at the 6-week postpartum visit.

Peripheral edema will be assessed by measuring the ankle circumference using a validated standardized technique to minimize errors[19]. A circumferential mark will be made with an indelible black marker 5 cm proximal to the right medial malleolus to ensure a consistent

location of measurements. A measuring tape will be placed such that is upper edge is in contact with the circumferential mark. Baseline circumferential ankle measurements will be made at 2 time points: at randomization and at day 5 (or at discharge, whichever occurs first).

Maternal weight change will be assessed using a single pre-specified weight scale at the time of randomization and at day 5 (or at discharge whichever occurs first).

In addition, 3 mL of maternal breast milk will be collected 44-48 h after the initial dose of Torsemide to measure the concentrations of the study drug, and 10 mL of maternal blood will be collected for serologic measurement of Torsemide concentrations as well as electrolyte profile. A baseline sample of 10 mL of maternal blood will also be collected at the time of hospital admission (as part of routine admission labs) and 44-48 h after the initial dose for metabolic profile. Samples will be stored at -20^{o} Celsius for pharmacokinetic analysis.

Sample Size

Data from Walters et.al.[17] and Goel et.al.[20] showed that 50% of women diagnosed with preeclampsia (but not gestational hypertension) prior to delivery have persistent postpartum hypertension requiring treatment 5 days after delivery (i.e. BP ≥150/100). To detect a 50% reduction in this rate, with 80% power and alpha-error of 0.05, a total of 118 (59 in each arm) patients need to be randomized. A total of 250 women would need to be approached for consent to accommodate an expected enrollment rate of 50%.

At MHH and LBJ hospitals, there are **7132 deliveries** per year as of 2013. Assuming a 10% rate of antepartum preeclampsia, there would be **>700 women per year eligible**. If we anticipate a 50% enrollment rate, then we should be able to complete this study in 1 year.

Statistical Tests

An intent-to-treat and/or per protocol analysis will be conducted. The rate of the primary outcome, persistent postpartum hypertension, will be compared between the intervention and control group using a log binomial (or Poisson in case of non-convergence) model to estimate relative risk and 95% confidence interval (CI). Each secondary outcome will be similarly analyzed using the best fitting generalized linear model with intervention group as the covariate. For all outcomes, we will report relative risks or differences and 95% CIs.

We will also conduct an interim Bayesian analysis of the primary outcome when 50% of enrollment has occurred to calculate probability of treatment benefit or harm. We will use a neutral prior distribution for the intervention effect that excludes implausible large treatment effects: Normal (0, SD=0.70) in the log RR scale (prior 95% interval for the RR of 0.23-4.35)[21]

Safety Assessment

Torsemide is generally well tolerated and adverse reactions are rare. In general, loop diuretics as a class may lead to profound diuresis and fluid electrolyte imbalances. This is particularly significant when the medication is administered intravenously or for long periods of time, with increased risk of symptomatic hypokalemia among patients treated with Furosemide.

However, in randomized clinical trials, hypertensive patients receiving Torsemide for 1 year had a mean decrease in serum potassium of approximately 0.1 mEq/L. The percentage of patients who had serum potassium level below 3.5 mEq/L at any time during the studies was similar between those receiving Torsemide (1.5%) than those receiving placebo (3%)[21,22].

Oral administration of Torsemide has been shown in controlled studies to lower both systolic and diastolic blood pressure. There is however, no significant orthostatic effect, and there is only a minimal peak-through difference in blood pressure reduction. The antihypertensive effects of Torsemide are greater in the African-Americans (a low-renin population). It has also been administered in conjunction with other antihypertensives (i.e. β-adrenergic blocking agents, ACE inhibitors, and calcium channel blockers). Adverse drug interactions have not been observed, and special dose adjustment has not been necessary[22].

Torsemide is contraindicated in patients allergic to sulfonylureas and those who are anuric[22].

There is no available data on the effect of Torsemide in lactation and it is not know whether Torsemide is excreted into the breast milk. Conversely, given that **it is the only category B** (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate or well-controlled studies in pregnant women) loop diuretic in pregnancy, the American Academy of Pediatrics labels Torsemide as “potentially safe in breastfeeding”. Indeed, both Furosemide and Bumetanide are category C (animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). However, given that loop diuretics as a class have the theoretic potential to suppress lactation, close monitoring is recommended[23].

Blood Draw with Venipuncture

Blood draws will be obtained from the maternal veins once during the study. Possible side effects of obtaining blood samples are pain, bruising, bleeding or infection at the blood drawing site and rarely, nausea or a lightheaded feeling. A skilled nurse will be retrieving the maternal blood. A maximum of 2 tablespoons of blood will be obtained at each timepoint.

Breast milk sampling

There are no known potential risks associated with sampling human breast milk.

Budget

Funding will be provided by the Division of Maternal-Fetal Medicine, from the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Texas Health Science Center at Houston [redacted]. Projected study costs are depicted in Table 4.

Informed Consent

A copy of the informed consent document in both English and Spanish to be used will be submitted by the Principal Investigator (PI) to the Institutional Review Board (IRB) for review and approval prior to the start of the study. A properly executed written informed consent shall be obtained from each patient prior to entering the study. All prospective study candidates will be given a full explanation of the consent form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the Investigator is assured that the individual understands the requirements of the study, the subject will be asked to sign the consent. The Investigator shall provide a copy of the signed and dated informed consent to the patient and the original shall be maintained in the patient's study files. Patients who do not sign the consent form will not be permitted to participate in the study.

Table 4. TROPHY Trial Budget

Institutional Review Board

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

Specification of Safety Parameters

The TROPHY trial is intended to evaluate whether the use of a loop diuretic (Torsemide) in the postpartum is effective in preventing persistent hypertension of ≥ 150/100 mmHg 7-10 days after delivery in women with preeclampsia prior to delivery. Torsemide has been approved by the Food and Drug Administration (FDA) for the management of hypertension either alone or in combination with other antihypertensives. Torsemide is routinely indicated for the treatment of edematous estates.

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

Management of Adverse Events

Any adverse events will be reported to the Committee for the Protection of Human Subjects (CPHS). The need for a Data Safety Monitoring Board will be deferred to the IRB.

Procedures in the Event of Abnormal Clinical Findings

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

Subject Confidentiality

Each study's subject anonymity will be maintained throughout the study. Prior to collection of the data a unique study number will be assigned to each case thus de-identifying the individual subject. Each study site will maintain a log of the study subject to the assigned study number.

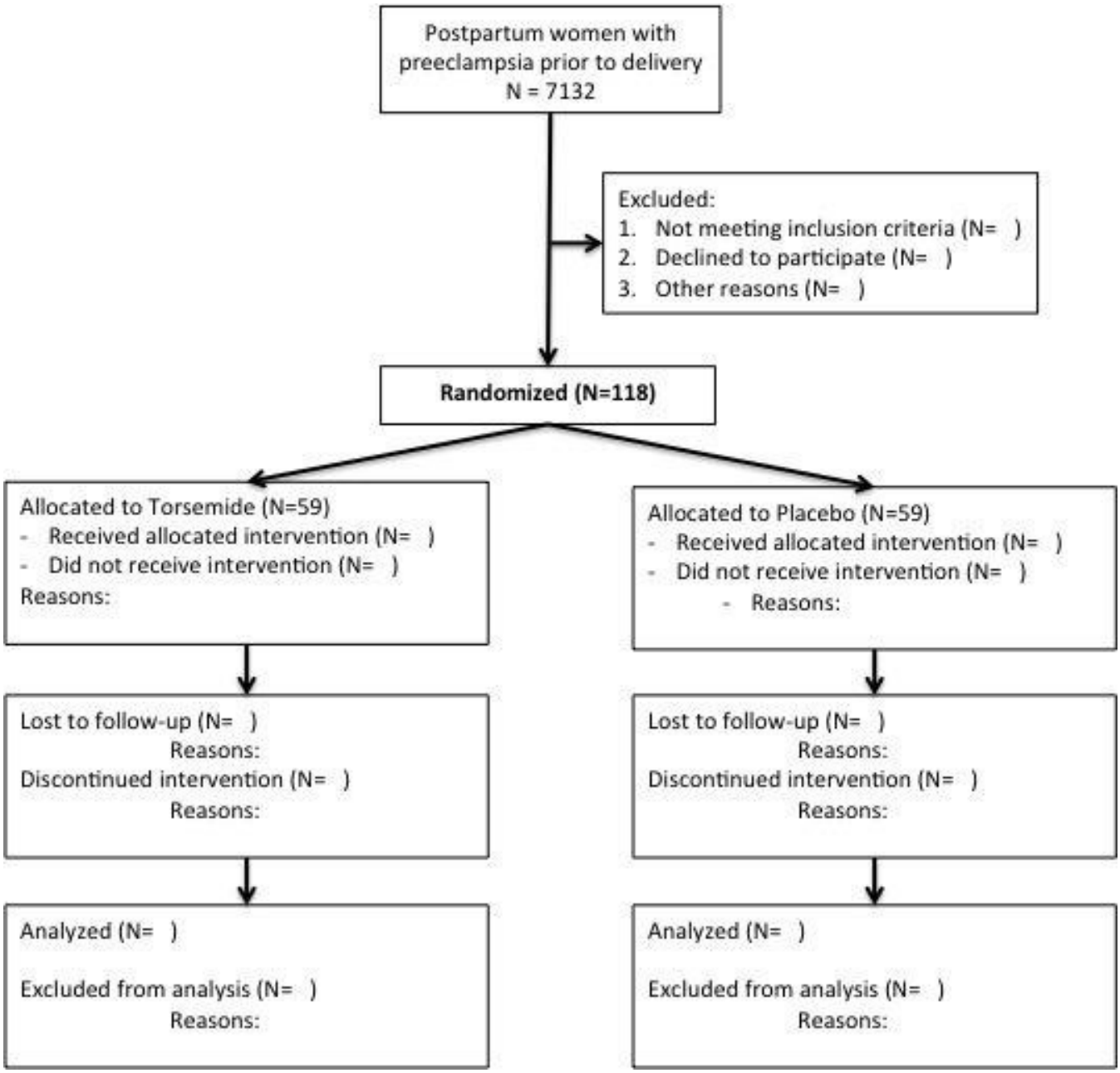

Figure 1. Study design and population

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