



GHP Study Protocol No. 4000

Oral antihypertensive regimens for management of
severe hypertension in pregnancy

Proposed Project Dates:

October 2013-December 2016

Full title of trial	Oral antihypertensive regimens for management of severe hypertension in pregnancy: a randomised trial comparing nifedipine, labetalol and methyldopa
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INTRODUCTION

Preeclampsia, and in particular severe preeclampsia, represents a significant risk to maternal health. Delivery of the fetus is the definitive treatment. Treatment with magnesium sulfate clearly reduces the risk for maternal seizures, eclampsia, and probably reduces maternal mortality. Treatment of severely elevated blood pressure should reduce the risk for maternal complications such as cerebral hemorrhage, cerebral edema and posterior reversible encephalopathy syndrome (PRES). Regimens for the acute treatment of severely elevated blood pressure that have been subjected to clinical trials have generally used medications administered intravenously, (eg. hydralazine, labetalol). While these regimens are effective in lowering blood pressure, they require venous access and have the potential to reduce blood pressure rapidly, destabilizing maternal hemodynamics at the expense of the fetal condition. Careful fetal monitoring is required.

An optimal antihypertensive regime for management of preeclampsia in low-resource settings would:

- Use oral drugs that are widely available
- Reduce blood pressure in a controlled and predictable manner so as not to destabilize the fetal condition
- Be cerebro-protective maintaining a normal cerebro-perfusion pressure and pulse pressure.
- Be free of significant side effects that could limit acceptability and utilization

A number of oral strategies have been suggested.¹ A few have been described in clinical practice.² Five trials of oral antihypertensive therapy for severe hypertension have been conducted.^{3,4,5,6,7} Yet no study comparing the three most common drugs used in pregnancy (labetalol, nifedipine and methyldopa) has been conducted. Evidence of the relative risks and benefits of different oral regimens will help develop guidance for antihypertensive use in pregnancy especially where multiple drugs are available.

Three drugs will be tested in this study: methyldopa, labetalol, and nifedipine. Each of these drugs has been used extensively in pregnancy and has a low incidence of medical complications.

Methyldopa is a central alpha agonist whose action results from adrenergic stimulation in the central nervous system and a resulting decrease in central adrenergic output. The drug has been in use for more than 20 years for the treatment of mild to moderate hypertension in pregnancy without any significant risk to maternal health. Long term follow-up for seven years in neonates have also shown it to be without identifiable adverse effects.^{8,9, 10} Individual clinicians report success in treating severe hypertension with methyldopa, (personal communication - Chris Redman, MD), however, there are few publications documenting the drug's efficacy in this population.

Labetalol is a combined alpha and beta blocker. In the oral form, the alpha component is much more active than the beta component due to differential metabolism of the isomer responsible for beta effect. Clinicians have reported success using oral labetalol to control severe hypertension with the dosages used in this protocol (personal communication - James Walker, MD). A randomized control trial compared oral labetalol and methyldopa.³ β -blockers are also associated with a decrease in the incidence of preeclampsia, (OR 0.73 [0.57, 0.94]^{11,12} a decrease in sFlt levels¹³ (an important mediator of endovascular pathology), and a decrease in the incidence of RDS in the premature neonate.¹⁴

Nifedipine is a calcium channel blocker and lowers blood pressure by vasodilation. Nifedipine is the drug most commonly used for acute hypertension at the participating centers and has been demonstrated to lower blood pressure in severely hypertensive

pregnant women. Treatment is commonly associated with headaches. Meta-analysis has suggested that treatment of hypertension with nifedipine may increase the risk of preeclampsia (OR 1.4 [1.06, 1.86])¹⁵ Treatment may be associated with a widened pulse pressure suggesting, with the incidence of headaches, that it may not be neuro-protective.¹⁶

Study Purpose

This trial will compare the efficacy, safety and side effects of these three oral regimens for management of severe hypertension in pregnant women. We hypothesize that nifedipine treatment of severe hypertensive parturient women is more effective than treatment with labetalol or methyldopa in controlling high blood pressure within six hours.

OBJECTIVES

Primary aim: To compare the efficacy of oral labetalol, oral nifedipine, and oral methyldopa for management of severe hypertension in pregnant women.

Secondary aims:

- To assess adverse outcomes and necessity for additional hypertensive treatment among women in the three study arms.
- To assess maternal and fetal outcomes among women in the three study arms

STUDY METHODS

Design

This is a pragmatic, open-label, randomised control trial of three oral anti-hypertensive regimens for women with severe hypertension in pregnancy. Women presenting with severe hypertension in pregnancy in two hospitals in Nagpur, India

will be randomised to one of three oral regimens: nifedipine, labetalol or methyldopa.

Study population

Pregnant women ≥ 18 years old and ≥ 28 weeks' gestation who have been determined to require pharmacological blood pressure control for severe hypertension defined as blood pressure $\geq 160/110$ mm of Hg, measured twice, 15 minutes apart with the woman sitting quietly for several minutes, the arm cuff at heart level, and diastolic pressure designated at the 5th Korotkoff sound, will be eligible for the trial. The relatively high entry criteria are chosen to avoid enrolling patients who might sufficiently improve without pharmacological treatment.

Two public hospitals in Nagpur, India – Government Medical College, Nagpur and Daga Women's Hospital, Nagpur – will be involved in this study. Together both hospitals have approximately 2,000 deliveries per month. Both hospitals have experience in the conduct of clinical trials, especially among this patient population. They encounter all the difficulties associated with low resource settings, but are also the site of an efficient and well run university department.

Number of Participants

We plan to recruit 894 participants (see sample size calculations below).

Inclusion Criteria

- Pregnant gestational age ≥ 28 weeks
- Systolic blood pressure ≥ 160 mm Hg OR a diastolic blood pressure of ≥ 110 mm Hg measured twice more than 15 minutes apart
- Able to swallow pills
- ≥ 18 years

Exclusion Criteria

- Indication for emergent cesarean or known fetal anomaly
- Anti-hypertensive therapy received in the past 12 hours
- History of eclampsia or other adverse CNS complication (e.g., stroke or PRES) in this pregnancy
- Actively wheezing at time of enrollment or history of asthma complications
- Known coronary artery disease or type I DM with microvascular complications or signs of heart failure or clinical dissection of the aorta

Identifying Participants

Initial contact with potential participants will be made when women present with severe hypertension. Posters will also be made available in the antenatal clinic and labour ward, aimed at women with pregnancy induced hypertension. Clinical staff will be made aware of the study and asked to notify appropriate patients.

Consent Procedures

Once the decision has been made clinically that a particular women requires treatment for severe hypertension, she will be formally approached by a member of the research staff. She will be given information leaflets in her own language and an opportunity to discuss enrolment with family members. If she decides to participate then she will be asked to sign a consent form. If the woman is unable to read, the form will be read and explained to her, and her consent will be indicated by a mark, such as the woman's thumbprint.

Those who agree to participate will be asked a few background and demographic questions after signing the consent form and completing the video recording. Information provided will be collected on the **Screening and Enrollment Form (Form 1)**.

All participants will be competent to give informed consent. The consent form will be available in English, Hindi, and Marathi.

Randomisation

After receiving written consent from the participant, the next consecutive, sequentially numbered opaque envelope will be withdrawn from the study dispenser. A card indicating the woman's treatment assignment will be included in the envelope. The card designating the treatment group will be attached to Form 1. The group assignments will be randomised independently using a computerised pseudo-random number generator; the randomisation will be stratified by centre.

Treatment Allocation

Sequence generation will be through a random sequence allocation computer programme. The provider will not be blinded to the treatment allocation.

The clinicians in both centres will undergo training in the use of the three treatment regimens. Guidelines for the management of treatment will be drawn up in collaboration with those in the centres so as to prevent operator bias through protocol deviations. The outcome data will be collected prospectively by study staff in order to ensure that the data collection is as complete as possible. Identical data tables will be used for the data monitoring committee and the final report in order to prevent reporting bias.

Study Interventions

Women in **Group A** will receive an initial dose of oral nifedipine 10mg. If blood pressure exceeds 155mmHg systolic OR 105 mmHg diastolic after 1h, an additional 10mg dose can be provided each hour for two additional doses (30 mg total).

Women in **Group B** will receive an initial dose of oral labetalol 200mg. If blood pressure exceeds 155mmHg systolic OR 105 mmHg diastolic after 1h, an additional 200mg dose can be provided each hour for two additional doses (600 mg total).

Women in **Group C** will receive an initial dose of oral methyldopa 1000mg. No additional escalation in dose in the first 6 hours will be given.

A range is provided in the threshold for dose escalation to permit input from clinical judgment. The maximum doses are based on the upper limits of effective dose range for each medication over 24 hours: nifedipine – 120mg; labetalol 2400mg; methyldopa – 2000 mg. The treatment goal (defined as 120-150 mmHg systolic and 70-100 mmHg diastolic) has been chosen based on NICE criteria. The relatively wide range between entry criteria and treatment goal should offer the best opportunity to discover differences in clinical response.

If the treatment goal (defined as 120-150 mmHg systolic and 70-100 mmHg diastolic) is achieved at 6h, treatment will be continued up to 24 hours postpartum unless deemed clinically unnecessary after delivery. The ongoing dose will be determined by the clinical care team based initially on the dose required over the first 6 hours and the clinical response after 6 hours. If the treatment goal is not achieved at 6h, women will receive the standard of care treatment for this indication. Women in the nifedipine group who do not achieve the treatment goal will continue to receive nifedipine 10mg. Women in the labetalol group who do not achieve the treatment goal will receive labetalol 200mg and women in the methyldopa group will receive either nifedipine 10mg or labetalol 200mg according to the treating physician's preference. In all cases, blood pressure monitoring will occur regularly as per standard hospital practice. During the treatment of a patient, the clinical team can determine that the study protocol should be discontinued due to 1) ineffective response resulting in clinically unsafe blood pressures or 2) significant side effects. Indications for stopping the treatment protocol will be recorded and study endpoints will be collected. Prior to and after enrollment in the trial, women in all groups should be treated with magnesium sulfate if clinically indicated and as per the standard treatment protocols at each facility. The use of magnesium sulfate and nifedipine together does not increase

the risk of serious magnesium-related side effects including hypotension (Magee et al 2005).

After the administration of the drugs, blood pressure and pulse will be recorded every 20 minutes. Blood pressure will be measured with an automatic digital blood pressure cuff. Oxygen saturation will be measured and recorded every 2h until 6h. The Glasgow Coma Scale will be administered by a research clinician at 0, 2, and 6h. AST (liver enzyme test), platelet count and creatinine will be performed at the start of antihypertensive treatment (0h), and 6 hours. Maternal side effects will be assessed at 0h, 2h, and 6h. Fetal heart rate will be recorded at 0 and 6h.

Study Outcomes

Successful outcome will be considered blood pressure that reaches the target (defined as 120-150mmHg systolic and 70-100 mmHg mm Hg diastolic) within 6h without an adverse outcome. Adverse outcomes include hypotension (systolic blood pressure, <120 mm Hg and/or diastolic blood pressure <70 mm Hg and fetal compromise), caesarean section for fetal distress within or up to 2 hours after the end of the study period, severe headache and severe headache requiring discontinuation of drug, or eclampsia.

Additional maternal outcomes:

- the number of BP measures above target range
- the number of BP measures below target range
- placental abruption
- maternal side effects associated with deteriorating maternal preeclampsia or the need to change drug regimen,
 - chest pain
 - dyspnea
 - headache
 - visual symptoms (flashes, diplopia)
 - epigastric or right upper quadrant abdominal pain

- nausea or vomiting.
- maternal mortality
- maternal morbidity during or up to two hours after the study period
 - eclampsia or seizure,
 - adverse CNS outcome (stroke, cortical blindness)
 - HELLP syndrome
 - pulmonary edema (O₂ sat < 90%, abnormal chest x-ray)
 - oliguria (<25 cc/hr for 2 hours)
 - disseminated intravascular coagulation
- Caesarean delivery
- Enrollment to delivery interval

Perinatal outcomes:

- stillbirth
- neonatal death
- admission to neonatal special care unit
- neonatal morbidity
 - Apgar < 7 at 5 minutes
 - intubation at place of delivery
 - mechanical ventilation beyond resuscitation
 - respiratory distress syndrome (RDS) requiring O₂ supplementation
 - abnormal cerebral ultrasound
 - convulsions
 - bradycardia (sustained HR < 100) beyond resuscitation and requiring intervention

Measures of the use of maternal health-care resources:

- number of days in the hospital
- admission to an intensive care unit or a high dependency unit
- mechanical ventilation (any)
- dialysis

- blood transfusion

Measures of the use of neonatal health-service resources:

- days in special care baby unit
- days of oxygen use
- days of mechanical ventilation

A post-study interview with the woman will be conducted once she is stable and prior to her discharge from the study hospital. Women will be interviewed and asked about their experience with pain and side effects. Women will be asked to rate their overall experience on a categorical five-point scale from 'very unsatisfied' to 'very satisfied'. Instruments will be informed by prior research on the acceptability of new medical technologies for delivery of magnesium sulphate among Indian women.

Data will be collected throughout the woman's admission, with data collection stopping postnatally at time of discharge or maternal death. No further follow-up is planned.

Pilot Study

Given the uncertainty of the effect of each of these drugs on this population, we will conduct a pilot study (n=30) prior to the start of the trial. The purpose of this pilot is to test the feasibility of the study protocol as designed. Women will be allocated serially to one of three oral antihypertensive regimens regimens: methyldopa (n=10), labetalol (n=10), or nifedipine (n=10).

The primary aim of the pilot study is to assess the three proposed drug regimens and, potentially, reveal the need for a lower dose. Methyldopa may not be effective for acute control of severe hypertension. However, in many settings where labetalol or nifedipine are not available, methyldopa is the oral drug of choice. Given our concerns about the slow onset and general lack of potency of

methyldopa, we are conducting a pilot study to assess whether it is appropriate to include it in the trial. If the success rate in any of the three arms is less than 30% (3/10) then the investigators will assess whether to include the regimen in the RCT. The secondary aims of the pilot are to (1) assess adverse outcomes and necessity for additional antihypertensive treatment among women in the three study arms; and (2) to evaluate data collection tools (including use of the Glasgow Coma Scale and assessments of women's attitudes post-treatment) in the subsequent trial.

Required ethical approvals for the pilot study have been obtained from Government Medical College Nagpur and the University of British Columbia.

Study Assessment and Data Collection Forms

Form 1: Screening Form. This form will determine a woman's eligibility for enrollment in the study. The form will also document basic demographic characteristics and obstetrical history.

Form 2: Monitoring Form (0-6h): This form will record the actual (rather than protocol) time for the administration of each dose. Assessment of blood pressure and pulse will be recorded every 20 minutes. Oxygen saturation will be measured and recorded every 2h. Maternal side effects including headache pain, nausea and vomiting, visual disturbances, urine output, right upper quadrant and epigastric pain will be assessed and recorded at the start of antihypertensive treatment (0h), 2h, 4h, and 6h. The Glasgow Coma Scale will be administered at 0, 2, and 6h by the attending research clinician. Although not specifically designed for this use, it is the best tool for assessment in this clinical environment. The utility of this tool for this trial will be assessed during the pilot study.

Form 3: Laboratory Results: This form will record the results of all laboratory tests. Liver enzyme tests, creatinine and platelet counts will be performed at 0h and 6 hours.

Form 4: Maternal Outcomes: The clinician will also note the final outcome of the woman including any interventions undertaken during labor and delivery. This information may be abstracted from patient charts if available.

Form 5: Neonatal Outcomes: The clinician will also note the final outcome of the baby including any interventions undertaken during labor and delivery. This information may be abstracted from patient charts if available.

Form 6: Exit Interview: The interview with the woman will be conducted once she is stable and prior to her discharge from the study hospital. This form will record her attitudes and opinions regarding the mode of treatment including experience with pain and side effects.

Form 7: Case Summary. Clinicians will complete a case summary form for each woman after she is discharged from the study. The form will summarize data recorded on other forms and confirm the number of doses administered, adverse events, and treatment discontinuation.

STATISTICS AND DATA ANALYSIS

Sample Size Calculation

The primary outcome will be control of high blood pressure (defined as 120-150mmHg systolic and 70-100 mm Hg diastolic) within 6h.

We hypothesize that nifedipine treatment of hypertensive parturient women will be more effective than labetalol or methyldopa in controlling high blood pressure (defined as 120-150mmHg systolic and 70-100 mm Hg diastolic) within 6h. Brown et al found that 83% of pregnant women with severe hypertension treated with nifedipine had successful lowering of blood pressure 110 to 169/80 to 109 mm Hg by 90 minutes without an adverse outcome.¹⁷ Our trial will enroll sicker patients and our goal is lower and lasting control. Based on the (scant) available literature, we hypothesize that nifedipine will control 75% of high blood

pressure within 6 hours and labetalol and methyldopa will be able to control 62.5% and 62.5%, respectively. As the subjects in the nifedipine study group will serve as a comparison group for both the labetalol and methyldopa regimens, the comparison of labetalol and nifedipine requires a sample size of 261 in each study group given a two tailed test, $\alpha=0.05$ and $1-\beta=80\%$, and a simple Bonferroni correction. Using the same statistical assumptions, with a nifedipine sample size of 261, the methyldopa study group requires 261 subjects. In order to account for loss to follow-up, we will enroll 894 women total (nifedipine: 298 women; labetalol: 298 women; methyldopa: 298 women).

Proposed Analyses

After the data are entered, they will be converted into an SPSS for Windows data file, reviewed for logical inconsistencies, cleaned, and analyzed.

For each of the regimens, we will calculate the following statistics:

- % of women who reach the target (defined as 120-150mmHg systolic and 70-100 mmHg mm Hg diastolic) within 6h without any specified adverse outcome (see above)
- % of women who reach the target (defined as 120-150mmHg systolic and 70-100 mmHg mm Hg diastolic) within 3h without any specified adverse outcome (see above)
- % of women who experience an adverse outcome. Adverse outcomes include hypotension (systolic blood pressure, <120 mm Hg and/or diastolic blood pressure <70 mm Hg and fetal compromise), caesarean section for fetal distress, severe headache or eclampsia.

- % of women who reach an intermediate target (defined as 120-159 mmHg systolic and 70-104 mmHg diastolic) within 6 hours without an adverse outcome.
- % of time systolic and diastolic blood pressure in target range

Logistic, Poisson and negative binomial regression models will be used as appropriate to estimate effect size (difference in attainment of treatment goal rates) with 95% confidence intervals. Adjustments in 95% confidence intervals will be made for important confounding variables and covariates including: mean arterial pressure at the initiation of therapy; heart rate at the initiation of therapy; mode of admission; evidence of abnormal laboratory results; history of chronic hypertension; diabetes (gestational or medicated); gestational age; and birth weight percentile. The primary analysis will be done according to intention to treat. If indicated, a secondary, per protocol analyses will be performed. Similar regression models will be used to compare the two study groups with respect to other important (secondary) variables.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

Trial Sponsorship

University of British Columbia

Trial Management

The study team at Gynuity Health Projects and GMC Nagpur will develop the study materials in line with the protocol. The day-to-day running of the study will be the responsibility of the Gynuity-Nagpur team who have extensive experience in conducting high quality studies in low resource settings. Prior to the start of the trial, the required local and national ethical approvals will be obtained by the Gynuity-Nagpur team who will also develop the trial documentation including data collection forms, patient information leaflet, consent form and trial standard

operating procedures (SOPs). Randomisation will be by means of random numbers centrally generated in distinct blocks. Randomisation and packaging will be by Gynuity Health Projects by staff not otherwise involved in the study. Gynuity-Nagpur will also train the local research team, manage routine trial logistics, establish a standard data entry system for trial data, supervise data entry, conduct quality checks on data entry system, and establish a backup system for trial database and relevant electronic files.

Enrolment, outcomes and side effects will be reviewed on a regular basis by coordinating staff at Gynuity Health Projects. Monitoring visits will be conducted at the commencement of the study, two times during study enrolment, and at the close-out visit of the study. If necessary, additional monitoring visits will be made to care any deficiencies in following study and data collection procedures. Data will be monitored, in strict confidence, by an independent data safety monitoring board (DSMB). A meeting of the DSMB will occur when approximately half of the study sample has been enrolled in the study.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

Individual Responsibilities

Dr. Beverly Winikoff and Hillary Bracken from Gynuity Health Projects will serve as co-investigators and collaborate on trial design, development of trial documents, management of the trial and write-up of trial results. Dr. Hillary Bracken will serve as a study monitor and will provide logistical support to the study sites and colleagues at the study sites in India.

Dr. Shuchita Mundle, Associate Professor, Department of Obstetrics and Gynaecology, Government Medical College, Nagpur will be a co-investigator and local study coordinator. She will oversee the day-to-day operation of the trial at Government Medical College, Nagpur and Daga Women's Hospital, Nagpur. She will also collaborate on trial design, development of study instruments and the analysis

of study results. She will be assisted by four research coordinators who will assist with the data collection, routine study management, and data entry at the two clinical sites.

Dr. Rajashree Patil, Associate Professor at Government Medical College, Nagpur, will be the Principal Investigator for Government Medical College, Nagpur. Dr. Vaishali Khedikar, Medical Superintendent at Daga Memorial Women's Hospital, will be the Principal Investigator for Daga Memorial Women's Hospital.

Dr. Laura Magee, University of British Columbia, and Professor Thomas Easterling, University of Washington, will assist in the design of the trial, development of study instruments, and analysis of trial results.

Trial Office

The Central Trial office will be based at the offices of Gynuity Health Projects in New York. They will provide support and training to the study team in Nagpur and, in liaison with, the trial statistician, will be responsible for randomisation, collection of data, data processing and analysis.

Data Management & Storage

At each hospital, patient files will be kept in locked cabinets with all identifying information removed. Signed informed consent forms will also be kept in locked cabinets, separate from the patient files. Only authorized study personnel will have access to these files. The original copy of all study forms will be sent to Gynuity Health Projects on a monthly basis and photocopies of each form will be maintained at each study hospital for five years.

Confidentiality

All evaluation forms and records will be identified using a coded number to maintain participant confidentiality. All records will be kept in a locked filing cabinet at the study hospital. Clinical information will not be released without the permission of the participant, except as required for monitoring by Gynuity Health Projects.

Data Monitoring Committee

An independent Data Safety Monitoring Board (DSMB) will be established to oversee the safety of participants in the trial. The terms of reference of the DSMB will be developed separately, based on the principles developed by the DAMOCLES group.

For safety purposes, interim analyses will be conducted when approximately half of the study sample have been enrolled (n=447). Recommendations will be made based on any findings of differences in primary outcomes or adverse events between the three study groups. The Haybittle–Peto boundary will guide the interim analysis and statistical stopping approach: If the interim analysis shows a probability of less than 0.001 that the primary outcome of the three treatments are different, then the trial will be stopped early. It is possible that only one arm might be discontinued without the need to discontinue the entire trial in the event of a safety issue in that arm.

As indicated above, the primary outcome is defined as the % of women who reach the target (defined as 120-150mmHg systolic and 70-100 mmHg mm Hg diastolic) at 6h without any specified adverse outcome.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Data Policy

The data from this study will be confidential until the database is closed at the end of the study. Following this the study investigators will have exclusive access to the data until the publication of the results in a journal. The consent form will include a clause for the woman to give permission for her anonymous data to be used for future research studies.

Publication

The study results will be published in an international medical journal at the end of the study, and presented at international professional and medical research meetings. The final publication will be open access. Study results will also be disseminated on the Gynuity websites and in in-house publications, including Gynuity's research briefs, both of which are designed to make scientific results accessible to a lay audience. In India, study findings will be presented at the annual meetings of the state and national conferences of the Federation of Obstetricians and Gynaecologists of India (FOGSI).

Intellectual Property/Commercial Exploitation

This research does not use any technology or other invention that is participant to patents or other forms of intellectual property protection. The proposed research will be conducted by a collaboration of three organizations and contracts will be drawn up between all relevant parties. The data could be used to register a new indication for the drugs involved in the trial, but the study team deems this unlikely given that all three drugs are already widely currently used. The study does not require the collection of any tissues or samples from human participants.

PHARMACOVIGILANCE

Risks to the Participants

Treatment with any antihypertensive medication is associated with the risk of hypotension or low blood pressure. These risks are extensions of the beneficial effects of the medications – treatment of hypertension, high blood pressure. Symptoms associated with low blood pressure may include dizziness, light headedness and fatigue. Low blood pressure can potentially adversely affect the fetus due to poor utero-placental perfusion associated with hypotension. These are, in general, dose dependent complications. Patient will be treated in a hospital

environment with close monitoring of blood pressure. To address the possibility of excessive under-treatment, aggressive oral regimens have been designed. The clinical team will remain "in charge" and have the autonomy to address issues of clinical under-treatment or concerns regarding impending over treatment.

The drug of choice for management of severe hypertension in pregnancy at the study sites is oral nifedipine 10mg-20mg. Headache is a common complication of treatment of blood pressure with medications that are pure vasodilators. Treatment with nifedipine is associated with the development of headaches (12-16%).^{18,19}

Historically, caution has been suggested for the use of β -blockers (labetalol) in the context of heart failure based on physiological assumptions regarding the impact on myocardial contractility. β -blockers are now considered to be fundamental to the pharmacological management of chronic heart failure. They are used with caution in patients with heart failure with hypotension. These patients are rare in pregnancy and would be excluded by BP criteria for entry.

Labetalol has a very low incidence of side effects. To the extent that beta activity is achieved, patient with acute asthma exacerbations could be adversely affected. Women with acute asthma will be excluded from the study. O₂ saturations will be monitored in all patients. Long-term treatment with beta blockers has been associated with intrauterine growth restriction. The clinical timeframe of this study is short and would not be expected to impact growth in a measurable way. Rare cases of drug induced hepatitis have been reported, (<1%). All patients will be monitored with liver enzymes.

Hepatitis is a rare complication associated with many medications and has been reported with the use of methyldopa and labetalol. Pregnant women with severe hypertension are at risk for the development of HELLP Syndrome that is, in part, manifested by elevated liver function tests. Methyldopa and labetalol have been used to treat hypertensive pregnant women extensively and for a long period of

time. Neither has been reported to increase the incidence of abnormal liver function tests in pregnant women treated for hypertension. Again, all patients will be monitored with liver function tests.

β -blockers (labetalol) can mask the adrenergic symptoms associated with hypoglycemia: tachycardia, palpitations, tremor and jitteriness. These signs of hypoglycemia are important symptoms for patients treated for diabetes with insulin. β -blockers do not mask cholinergic symptoms such as sweating. Few subjects are anticipated to be treated with insulin. All women will be managed in the hospital with close observation.

Treatment with any medication includes the risk for unanticipated allergic or hypersensitivity reactions.

Protection against risk

Clinical monitoring will occur throughout the treatment, with blood pressure and pulse checked at least every 20 minutes (or as per standard practice at each facility). Oxygen saturation will be measured and recorded every 2 hours. Liver enzymes will be monitored in study subjects. Study treatment will be discontinued if clinically indicated, however data collection will continue until discharge from the study hospital.

Potential benefits

Women participating in the study may benefit from the intensive clinical monitoring associated with study participation. Women may also derive satisfaction from facilitating the development of an oral drug regimen for management of severe hypertension in pregnancy.

Benefits to society include the potential availability of an oral drug regimen that can be offered to more women and in more settings. This may increase the availability of services for the treatment and prevention of preeclampsia and eclampsia in India.

Alternatives to Participation

Any woman who declines to participate or withdraws from the study will be offered the standard care for the treatment of her condition. Her refusal will not affect her care. Women may refuse to answer any question at any time during the study period.

Regulatory Approvals

Prior to the start of the trial, the required local and national ethical approvals will be obtained by Gynuity Health Projects in collaboration with Dr. Shuchita Mundle, Government Medical College, Nagpur, India. Ethical and research approval will be obtained from the University of British Columbia, Government Medical College Nagpur, the Indian Council of Medical Research and any other relevant local authorities. All study staff will undergo a study training organized by Gynuity Health Projects prior to the start of the trial. A Data and Safety Monitoring Committee will be convened.

Study Monitoring

Dr. Mundle will conduct a monthly audit to confirm consent processes and study procedures are followed and all consent forms are properly signed, dated, and stored at both study sites. During regular monitoring visits, Gynuity staff will also confirm whether proper consent procedures and good clinical practice are maintained. Results of monitoring visits will be recorded in monitoring reports and circulated to study staff and discussed at a staff meeting at the end of the monitoring visit.

Adverse Events

When an adverse event (AE) occurs, it is the responsibility of the Principal Investigator in Nagpur to review all documentation. If the AE meets the criteria of serious (see below) it should also be recorded on the SAE form and faxed / e-mailed to the Gynuity Health Projects (GHP) SAE desk in New York. At the SAE

desk, GHP staff will assess the severity, relatedness and seriousness of the event and determine whether or not the event should be reported as a Suspected Unexpected Serious Adverse Event (SUSAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR). Should the event be determined to qualify as a SUSAE or SUSAR, GHP will provide the co-investigators and members of the Data Monitoring Committee with a complete report of the event. In all cases, GHP and the collaborating partners will duly inform the relevant ethics committee and licensing authority as required by current legislation.

Once a year, GHP will prepare an annual safety reporting describing all Serious Adverse Events (SAEs) and related incidents, Dr. Mundle and Hillary Bracken will be responsible for filing the report with the relevant ethics committees and licensing authorities in India and the University of British Columbia, as required by current legislation.

Serious adverse events (SAEs)

A serious adverse event is defined as one causing:

- Permanent or serious disability;
- Additional threat to life; or
- Death.

All serious adverse events must be reported by the investigator within 24 hours of her/his becoming aware of them to the study coordinator at Gynuity Health Projects. This reporting can be done by telephone, fax or e-mail. The report of a serious adverse event must always be followed by a detailed written report containing patient information, description of the event or problem, relevant laboratory results, and information pertaining to pre-existing medical conditions. As described above, each study participating hospital will be supplied with SAE forms to complete as needed.

When reporting a serious adverse event, the on-site investigator should protect the patient's confidentiality by excluding names or addresses. The unique subject code should be used in the report and the investigator should retain the code to facilitate verification of data by the study coordinator or drug regulatory authority.

REFERENCES

- ¹ S. T. Vermillion, JA Scardo, RB Newman, SP Chauhan. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol.* Vol 181, No. 4, pp. 858-61.
- ² D.J. Tuffnell, D. Jankowicz, S.W. Lindow, G. Lyons, G.C. Mason, I.F. Russell, J.J. Walker. Outcomes of severe preeclampsia/eclampsia in Yorkshire 1999/2003. *BJOG*, July 2005, Vol 112, pp. 875-880.
- ³ Moore MP, Redman CWG. The treatment of hypertension in pregnancy. *Current Medical Research and Opinion* 1982;8:S39-S46.
- ⁴ Voto L, Lapidus A, Neira J, Margulies M. Atenolol vs alpha methyldopa in the treatment of hypertension in pregnancy. In: 5th International Congress for the International Society for the study of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, UK. 1986:138.
- ⁵ Voto LS, Zin C, Neira J, Lapidus AM, Margulies M. Ketanserin versus alpha methyldopa in the treatment of hypertension during pregnancy: a preliminary report. *Journal of Cardiovascular Pharmacology* 1987;10(Suppl 3):S101-S103.
- ⁶ Hall DR, Odendaal HJ, Steyn DW, Smith M. Nifedipine or prazosin as a second agent to control early severe hypertension in pregnancy: a randomised controlled trial. *BJOG.* 2000 Jun;107(6):759-65. PubMed PMID: 10847232
- ⁷ Brown MA, Buddle ML, Farrell T, Davis GK. Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. *Am J Obstet Gynecol.* 2002 Oct;187(4):1046-50. PubMed PMID: 12389003.
- ⁸ Ounsted MK, Moar VA, Good FJ, Redman CW. Hypertension during pregnancy with and without specific treatment; the development of the children at the age of four years. *Br J Obstet Gynaecol.* 1980 Jan;87(1):19-24.
- ⁹ Report of the National High Blood Pressure Education Program Working Group on High Blood in Pregnancy. *Am J Obstet Gynecol* 2000;183:S1–22.)
- ¹⁰ Mutch LM, Moar VA, Ounsted MK, Redman CW. Hypertension during pregnancy, with and without specific hypotensive treatment. II. The growth and development of the infant in the first year of life. *Early Hum Dev.* 1977 Oct;1(1):59-67.

- ¹¹ Easterling TR, Brateng D, Schmucker B, Brown Z, Millard SP: Prevention of Preeclampsia: A randomized trial of atenolol in hyperdynamic patients prior to the onset of hypertension. *Obstet Gynecol* 1999; 93(5): 725-33.
- ¹² Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD002252. Comparison 4.1
- ¹³ Carr DB, Tran LT, Brateng DA, Kawamura C, Shofer JB, Karumanchi SA, Easterling TR. Hemodynamically-directed atenolol therapy is associated with a blunted rise in maternal sFLT-1 levels during pregnancy. *Hypertens Pregnancy*. 2009 Feb; 28(1): 42-55.
- ¹⁴ *Eur J Obstet Gynecol Reprod Biol*. 2000 Jan; 88(1): 15-26. Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials.
- ¹⁵ Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD002252. Comparison 4.6
- ¹⁶ Martin JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol*. 2005 Feb; 105(2): 246-254.
- ¹⁷ MA Brown, M Buddle, T Farrell et al. Efficacy and safety of nifedipine tablets for the acute treatment of hypertension in pregnancy. *Am J Obstet Gynecol*. 187 (4): 1046-1050.
- ¹⁸ Stephen T. Vermillion MD, James A. Scardo MD, Roger B. Newman MD, Suneet P. Chauhan MD A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol* 1999; 181: 858-61.
- ¹⁹ Raheem I, Saaid R, Omar S, Tan P. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. *BJOG* 2012; 119: 78–85.