IMPROVE (Identifying Methods for Postpartum Reduction of Vascular Events): Pilot Randomized Controlled Trial

DETAILED METHODOLOGY AND ANALYSES

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Appendix 3. IMPROVE Pilot Randomized Controlled Trial Detailed Methodology and Analyses

1.0 Overall study design:
The IMPROVE-Pilot Study is a single-centre, single-blind, parallel, randomized controlled trial with a one-to-one intervention to control allocation.

2.0 Participants Eligibility Criteria:
2.1 Inclusion Criteria: Participants must meet all of the following:
a) adult women aged 18 years or older;
b) diagnosis of a HDP (i.e., preeclampsia, eclampsia or gestational hypertension);
c) delivering at The Foothills Medical Centre (FMC) in Calgary, Alberta;
d) ability to read, write, understand, and provide informed consent in English; and
e) have telephone access.

Justification: Telephone access is integral to the implementation of the study intervention as a component of the counselling intervention. Although 90% of Canadians report access to a cellular phone, the number of women who do have telephone access will be assessed in order to ensure no evidence of selecton bias[1].

2.2 Exclusion Criteria: Individuals with any of the following will be excluded:
a) pre-existing vascular disease (coronary artery disease [i.e., stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass surgery], cerebrovascular disease [i.e., ischemic stroke or transient ischemic attack], or peripheral arterial disease [i.e., known abnormal ankle-brachial indices, symptoms of intermittent claudication, or bypass surgery to the extremities]);
b) chronic hypertension;
c) diabetes (type 1 or type 2);
d) pre-pregnancy kidney disease;
e) planning another pregnancy within one year;
f) counselling may not be appropriate (i.e., impaired cognition);
g) live more than 200 km outside the Calgary region; and
h) planning to move outside the Calgary region within one year of randomization.

Justification: The above medical conditions are excluded, as there already are either existing recommendations for vascular prevention (e.g., use of specific pharmacotherapy) or lifestyle programs available (e.g, diabetes). This study will exclude women who are planning a pregnancy within one year, as the study intervention is a full-year duration and weight loss during pregnancy remains controversial[2]. This is unlikely to reduce study recruitment or affect external generalizability, as obstetrical societies recommend spacing pregnancies by at least eighteen months to two years to minimize preeclampsia recurrence[3]

3.0 Planned trial interventions:
3.1 ***Intervention:*** In addition to standard care, participants randomized to the intervention arm will also receive the CardioPrevent® Program. This is a 1-year, evidence-based behaviour change lifestyle program that consists of 25 contacts (in person, by phone and in groups) with a trained lifestyle counsellor to facilitate desired lifestyle behaviours within the participants' own social context.
3.2 ***Control:*** Standard postpartum clinical care through the participants' usual healthcare providers.
3.3 ***All Participants:*** Participants in both arms will receive educational material about the risk of CVD, and CVD prevention for women with HDP from the Preeclampsia Foundation ***(Appendix 6)***.
3.4 ***Duration of Treatment:*** The treatment period is one year. This duration is clinically important for two reasons. First, longer behaviour change interventions have greater success with maintenance of healthy behaviours compared with shorter interventions[4]. Thus, the CardioPrevent® behaviour change

intervention was specifically designed to be one year[5]. Second, maternity leaves in Canada are generally one year. Women in the intervention arm will be in the "relapse prevention" phase of the behaviour change intervention as they return to work. The CardioPrevent® postpartum participants to date have emphasized the importance of this phase.

3.5 *Duration and frequency of follow up*: All study participants will complete in person clinical assessments at baseline, six months, and one year after their randomization date. All study assessments will be done on an individual basis, by a research assistant who is blinded to group assignment.

4.0 Study Outcomes:

4.1 Primary outcome:

a) *Study feasibility*: Acceptance of the study by women with HDP (i.e., feasibility) measured by all of the following: recruitment rate of ≥ 20% over a 6-month time period (as per weekly recruitment logs –); participant adherence of ≥ 80% to the lifestyle program (i.e., 20/25 contacts with counsellor completed); overall study completion rate of ≥ 75% of participants; and participant satisfaction score of ≥ fair on the Client Satisfaction Questionnaire at the end of study[6].

b) *Implementation and fidelity of CardioPrevent® at a second centre* measured by standardized audits as well as similar clinical outcomes between sites

4.2 Secondary outcomes:

a) Comparison of the following *clinical outcomes* between both study arms at one-year of follow-up: weight, body mass index, waist-to-hip ratio, smoking status, postpartum depression, blood pressure, fasting lipids, fasting glucose, HbA1C, urine albumin to creatinine ratio, metabolic syndrome z-score and CVD risk.

b) *Microvascular function*: mean changes from baseline to one year of follow-up compared between groups for the following measures: flow mediated dilatation (FMD), brachial artery hyperemic velocity and peripheral arterial tonometry (PAT).

C) Changes in physical activity and dietary behaviour.

4.3 Measurement of study outcomes*:** Standardized assessments will be performed by a trained research assistant (blinded to group allocation) as outlined below, and in the Schedule of Measures ***(Appendix 8).

4.3.1 Clinical measures:

a) *Blood pressure*: Blood pressure is measured in a seated position after a five-minute rest period using an automated non-invasive blood pressure monitor (BPTru®) that automatically performs up to six measurements, discards the first reading, and displays the average of the subsequent readings[7]. Treatment of hypertension is determined by a review of current medication use.

b) *Body composition*: Height and weight are measured for the determination of body mass index (BMI) using a standardized protocol[8]. Waist and hip circumferences are measured using standard anatomical landmarks following the World Health Organization's recommendations[9].

c) *Smoking status*: Current smokers are defined as individuals who have smoked any cigarettes (even a puff) in the past seven days[10]. Claims of non-smoking are verified using a carbon monoxide analyzer (Bedfont Smokerlyser) with CO levels < 10ppm confirmatory for non-smoking[11].

d) *Medication Use*: It is measured by having participants list the name and dosage of all prescription medications they are currently taking. Participants are asked to bring their medications with them to each visit for verification. Medication adherence with MAQ-8 questionnaire[12].

e) *Metabolic Syndrome*: Using the ATP III Criteria for Metabolic Syndrome, all five variables (i.e., waist circumference ≥ 88cm; triglycerides ≥ 1.7 mmol/L; HDL < 1.3 mmol/L; BP ≥130/≥85 mmHg; and fasting glucose ≥ 6.1 mmol/L) will be recorded categorically[13] and also scored as a continuous variable as a z-score (a measure of overall CVD risk) in lifestyle intervention studies[14-16].

f) *Breastfeeding / Infant Feeding*: will be self-reported and categorized as: no breastfeeding or expressed breast milk (EBM); breastfeeding/EBM and formula, exclusive breast milk. The duration

of breastfeeding will also be reported for use in statistical analyses given the effects of lactation on vascular health[17, 18].

4.3.2 Laboratory measurements:

a) *Fasting blood tests:* Will be collected after a minimum 8-hour fast. Plasma lipids (total cholesterol [TChol], HDL-C, LDL-C, triglycerides, calculated TChol to HDL ratio), creatinine, glucose and HbA1C will be analysed using standardized laboratory procedures at the FMC lab[19].

b) *Urine tests:* A random urine sample will be analysed for the albumin to creatinine ratio.

4.3.3 Questionnaires: will be used to measure the following

a) *Postpartum Depression*: The Edinburgh Postnatal Depression Scale[20, 21].

b) *Diet*:The REAP (Rapid eating assessment of patients)[22] and three days of prospective food logs[23].

c) *Physical Activity*: the IPAQ-short form[24], activity logs[25], and by accelerometers[26].

d) *Participant Satisfaction*: the Perceived efficiency in patient-physician interaction scale[27].

e) *Social Support*: Multidimensional scale of perceived social support[28]and perceived stress scale[29].

4.3.4 Cardiovascular Risk: will be measured using the Lifetime Cardiovascular Risk Score[30].

***4.3.5 Microvascular Function*:** These tests will be performed by an experienced technician and C. Wen (PhD Student) in the experienced Anderson Lab (Mozell Vascular Function Lab) at the University of Calgary using standardized techniques[31]. Participants will be asked to abstain from caffeine or nicotine for at least 2 hours prior to the testing. Participants will then rest in a temperature-controlled room (22 degree Celsius) for 15 minutes prior to beginning the protocol[31].

a) *Flow Mediated Dilatation (FMD)* of the right brachial artery: Using Philips IE 33 (high resolution > 10 MHz linear array ultrasound probe), B mode imaging and pulsed wave Doppler are used to measure the brachial artery diameter at baseline and after 5 minutes of occlusion. For the occlusion, a blood pressure cuff will be placed on the arm above the antecubital fossa with a five minute occlusion time (cuff inflated to 50 mmHg above the participant's systolic blood pressure). Doppler recordings include 15 seconds before and after the cuff pressure is released. Of note, the sublingual nitroglycerine response will not be assessed due to unclear safety of nitroglycerine in lactation.

b) *Hyperemic velocity (HV):* As part of the FMD testing, hyperemic velocity will be measured for 30 seconds after cuff pressure is released. This is determined by the peak of the velocity-time integral after the first complete velocity envelope. Of note, higher values represent better microvascular dilatation.

c) *Peripheral Arterial Tonometry (PAT):* PAT consists of measurement of pulse wave amplitude responses using a finger tip (right and left index finger) plethysmographic device (Itamar-medial Inc., Caesaria, Israel).

5.0 Methodology:

5.1 ***Participant allocation and randomization:*** In order to maximize recruitment rates, a research nurse at FMC will screen admitted patients on the obstetrical wards for eligibility for the trial prior to discharge from hospital. The research nurse will then approach women who meet the eligibility criteria to explain the study and determine whether the women are interested in participating in the study. If a woman is interested, she will be provided with written information on the study. After providing informed consent, she will be given an appointment for the baseline assessment at approximately six weeks (range of 6 to 12 weeks) postpartum. After discharge from the hospital, participants will be sent reminder information about the study and the date of the baseline visit.

At the baseline assessment visit, consecutive women will be randomized to either the intervention or control arm in a 1:1 allocation, with use of permuted blocks of variable length (2, 4 or 6) using an on-line central randomization system through the Data Management Services group at the Libin Cardiovascular Research Institute. The on-line randomization program will ensure participant eligibility and maintain concealment of allocation. The randomization schedule will be prepared by an independent statistician using a computer-generated random number scheme.

5.2 Blinding - the outcome assessor and statistician: The nature of the intervention (i.e., the CardioPrevent® cognitive-behavioural lifestyle counsellor) does not lend itself to blinding of the participant. However, the research assistant responsible for the outcome assessments will be blinded to each participant's group allocation and will be instructed not to ask any questions pertaining to the study intervention. The study statistician will also be blinded to group allocation.

5.3 Contamination: Contamination is unlikely, as individuals allocated to the control group will not have direct access to the cognitive-behavioural lifestyle counsellor. It is possible, however, that participants may know other women involved in the study. Consequently, participants in both arms will also be instructed not to share their study information with other participants.

5.4 Co-interventions: As participants will know their allocated group, they may relate this information to their usual healthcare providers. It is therefore possible that, if in the control group, the participants' healthcare providers may provide additional lifestyle modification recommendations. Based upon the research of two co-investigators, this is unlikely to have a great effect on the study results, as few healthcare professionals (<10%) counsel women with HDP on future chronic disease risk[32], and physicians generally spend less than 8 minutes counselling patients on CVD[33]. To further limit this potential bias, information on HDP and CVD will be provided to participants in both arms at the end of the study. Co-interventions with other drug, medical or dietary therapies will be at the discretion of the participant's usual healthcare provider and will be measured and compared in both groups. While the PreVASC clinic (a postpartum vascular prevention clinic) exist for women with HDP in Calgary, as this is not standard care across Canada, in order to minimize bias from the effect of the clinic itself, clinicians will be asked not to include trial participants in PreVASC until study completion. Furthermore, an environmental scan of resources in Calgary yielded no specific lifestyle programs for postpartum women with HDP.

5.5 Adherence / Attrition: All attempts will be made to ensure complete follow up by all participants through in-person, telephone, and email reminders. To increase attendance at scheduled follow-up visits, we will provide reimbursements for parking and childcare costs (if needed), and include only women who live in the immediate Calgary region.

5.6 Selection bias: To minimize selection bias, a standardized systematic process for screening all women delivering at FMC for eligibility will be implemented. Specific reasons for non-participation will be recorded (ineligibility and main reason for declining). In addition, pragmatic eligibility criteria were developed to ensure external generalizability.

5.7 ***Anticipated loss to follow-up:*** In the Family Heart Health Study (non-postpartum individuals), at one year, the rate of loss to follow-up was 27% in the standard care arm and 24.6% in the intervention arm (25% cited "too busy" or "not interested")[34]. In the DEBI postpartum trial, however, there were higher rates of participant completion of the 1-year study: 90% in the intervention arm and 80% in the control arm; and 97% of participants in the intervention arm were "satisfied" with the program[35]. Thus the target participant completion rate for the IMPROVE-Pilot study is ≥ 80% (i.e., LTFU of <20%). To reach this target, we have also included reimbursements for parking and childcare costs for the baseline, 6- and 12-month outcome assessment visits. In addition, we have increased the study sample size by 30% to account for potential LTFU common to lifestyle intervention studies[34].

5.8 Sample size: A total of 84 women will be recruited (42 in each arm). This is based upon a minimally clinically important difference in BMI of 1 kg/m^2 supported by the literature on the association between BMI and CVD[36, 37] and by the finding from the Canadian PE-NET cohort demonstrated that women with HDP actually increase their BMI by 1 year postpartum[38]. Results of CardioPrevent® in other populations of women resulted in SD of 1.4-2.3[34]. The lower SD of 1.4, alpha of 0.05 and power of 80% yields 32 women per arm (64 total). We increased this by 30% to account for loss to follow-up in other postpartum studies[35].

5.9 Recruitment: There are over 7000 deliveries per year at the FMC. Using a conservative estimate of 7% prevalence of HDP (as it is a tertiary care referral centre), approximately 245 women (10 per

week) will have HDP over our 6-month recruitment period. We anticipate recruiting 2-3 eligible women per week to reach our target sample size in 6 months. Recruitment will be monitored on a weekly basis with review of recruitment logs that monitors reasons for non-participation and ineligibility**.** Should recruitment rates from the in-patient wards alone be below anticipated targets, we will engage alternate modes of participant recruitment through outpatient clinics (Maternal Fetal Medicine and Obstetric Medicine) where we have co-investigators and recruitment infrastructure.

6.0 Statistical analyses: At the end of the study, the following will be analyzed.
Participant characteristics will be summarized with standard descriptive statistics. *Feasibility outcomes* will be summarized as frequencies with % and presented as per CONSORT Guidelines[39], between group differences will be tested using Pearson's chi-square or Fisher's exact test. Non-adherence patterns will be assessed. *Quality assurance (QA) measures:* Mean with standard deviation (SD) scores from the three QA checks per counsellor will be compared to Ottawa standards using a Student's t-test. *Clinical outcomes:* Changes from baseline will be summarized using: means with SD; medians with interquartile ranges; and counts with % where appropriate. Exploratory analysis comparing outcomes between arms will be done with T-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. *Planned subgroup analysis:* will be performed to compare severity of HDP (gestational HTN, non-severe preeclampsia [PE], early onset PE < 34 weeks, or clinically severe PE) on clinical and vascular outcomes. An *intention-to-treat* principle will be followed. All *P-values* will be two-sided, at a significance level of 0.05. *Missing data* will be imputed.

7.0 Trial Management:
The trial will be managed through the Libin Cardiovascular Institute. A 0.4 FTE Research Coordinator will be responsible for the day-to-day conduct of the trial under the supervision of the study PI, including: REB applications; recruitment reports; and data quality reviews. A 0.1 FTE Research Nurse responsible for screening participants and obtaining informed consent. Data will be managed by Libin's Data Management Service, including: development of database; development of electronic case report forms; on-line randomization; and data maintenance and storage.

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