A Randomized Trial of a Low Carbohydrate Diet Versus the Current Recommended 2015-2020 Dietary Guidelines to Improve Health Outcomes in Obese Postpartum Women

A **S**tudy of a **L**ow-Carbohydrate Diet to **I**mprove **M**aternal Health after Childbirth (SLIM)

Clinical Research Protocol
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1. **Introduction/Background/Purpose:**

The United Nations has declared that chronic non-communicable diseases such as heart disease and diabetes pose a greater health burden worldwide than do infectious diseases, contributing to 35 million deaths annually (1). The incidence of obesity has risen continuously over the last several decades. According to data from the National Health and Nutrition Examination Survey, the prevalence of obesity among women of reproductive age (20–39-years old) in the United States of America is nearly 31.8% (2). Excessive weight gain during pregnancy and postpartum retention of pregnancy weight gain are significant risk factors for continued obesity later in life (3). Pregnancy is often described as a window to future health, as many women are diagnosed with metabolic conditions for the first time in their life during pregnancy. Obesity syndrome, otherwise known as metabolic syndrome, is associated with the development of chronic diseases, such as type 2 diabetes, chronic hypertension, and heart disease. The underlying causative factor of metabolic syndrome is a state of insulin resistance. Due to physiologic changes that occur during pregnancy, women may be at increased risk for developing insulin resistance during pregnancy making the postpartum period an ideal time to intervene to prevent and treat this epidemic(4).

Although there is a strong desire to lose weight in the postpartum period, many women struggle to actually lose weight. Low carbohydrate diets have been compared with low fat, energy restricted diets, the standard American style diet as recommended by the United States Department of Agriculture Dietary Guidelines for Americans (5-14). A meta-analysis of five trials with 447 participants (13) and a 1-year trial involving 311 obese women (7) suggested that a low carbohydrate diet is a reasonable alternative to a low fat diet for weight loss and may have favorable metabolic effects, including improvement in insulin resistance (14). In addition, it has been reported that compared with a low fat diet, a low carbohydrate diet program had better participant retention and greater weight loss (9).

The X-PERT weight loss program offers a structured patient centered educational program for a low carbohydrate diet through a combination of resources, which include in person group meetings, online educational materials, and printed educational materials (15). Some research has shown that greater weight loss and diet adherence is achieved when there is a behavioral component added to a diet plan (16). For example, it has been reported that weight loss was substantially greater in participants who attended group sessions regularly (17). We propose that a low carbohydrate diet with a behavioral component is associated with improved insulin sensitivity as compared to the standard of care obesity education that is part of routine postpartum care.

2. **Concise summary of project:**

This trial will be a comparative non-blinded randomized controlled trial in obese postpartum women.

Three groups will be compared during the postpartum period:

1. Control Group: Standard of Care

2. Intervention A: Low carbohydrate diet with printed materials and online resources, provided by X-PERT weight loss program.
3. Intervention B: Low carbohydrate diet with a behavioral component consisting of twelve weekly meetings with an X-PERT trained professional supported with printed materials and online resources.

The number of subjects studied will be 321 subjects at UTMB.

3. Study procedures:

Eligible subjects will be approached, and those who consent will be randomized to one of the three groups described above.

All groups will receive standard postpartum care. In addition, all subjects enrolled in the study will have three study visits at which time a blood and urine sample will be collected. Subjects may be contacted by trained research personnel throughout the study period to remind subjects of upcoming appointments.

Subjects enrolled in the intervention groups (Intervention A&B) will receive printed materials and have access to online resources provided by X-PERT weight loss program throughout the course of the study.

- The printed material is approximately 200 pages in length and includes 12 topic-specific sections with information on nutrition, lifestyle, health, tools and tips for maintaining diet, recipes, and food diary templates.
- The online resource can be accessed by an application on a phone or tablet or through the internet via a computer.
- The online resource includes 12 informational sessions (designed to cover topics in a similar fashion to the group sessions), a digital copy of the printed materials, option to take part in an online form, and the option to record personal health information, such as height, weight, monitoring of health points (such as waist circumference, lab values, etc), carbohydrate intake, eating frequency, and dietary approach.
- Subjects will access the online application via a de-identified study related email address. This email address will be provided to the subject; a personal email address will not be used. In order to access the online application, the subjects will input a study related email address and a password that they chose. The email address will also serve as the username for the online application. The online application has the ability to enter personal information, as mentioned in the previous bullet point. The personal health information can be entered into the online application as often as any subject choses, including no entry at all. The subjects are not required to enter personal health information into the online application, rather subjects are given the option.

Additionally, subjects enrolled in Intervention B will have 12 weekly group sessions with an X-PERT trained professional. The group sessions will last approximately 1.5 hours and have no more than 20 subjects enrolled in each group. Subjects will be welcome to bring their infant to each group session. A babysitter will not be provided

so the subject will be responsible for taking care of her own infant. Breastfeeding or formula feeding during the group session will be encouraged. The group session is available to research study participants only; besides the infant, no additional family members will be allowed. If enrolled in Intervention B, subjects will have up to 15 in person visits.

Blood and urine samples will be collected at each study visit. The first study visit will occur at 2-3 weeks postpartum. The second study visit will occur at 3 months postpartum (+ 3-week window). The third study visit will occur at 6 months postpartum (+ 3-week window). All samples will be collected while the patient is fasting (not eating for at least 8 hours). A standard 4oz sterile urine collection cup will be provided for each urine sample. Urine will be checked for glucose and ketones by dipstick. Approximately 20mL of blood will be collected with each sample. The blood samples will be used for the following tests:

- Hemoglobin A1c (HgA1c)
- Lipid panel
- Homeostatic Model Assessment (HOMA) test for insulin sensitivity or resistance: we will measure fasting insulin and glucose levels. Fasting will be defined as the last meal more than 8 hours before testing (i.e. overnight fasting). We will be using the following computation to calculate HOMA.

$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{22.5}$	$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{405}$
$\text{HOMA-}\beta = \frac{20 \times \text{Insulin}}{\text{Glucose} - 3.5}\%$	$\text{HOMA-}\beta = \frac{360 \times \text{Insulin}}{\text{Glucose} - 63}\%$
Glucose in Molar Units mmol/L	**Glucose in mass units mg/dL**

Blood and urine samples will be taken to the lab to complete the above-mentioned tests and/or stored at -80^{0}C in our perinatal research department for later processing. The blood and urine will be stored in the perinatal research department with the potential for future metabolic testing that relates to this research study. Only the PI and research staff involved with this study will have access to the stored samples.

All subjects will receive a participant ID number. Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database. Several data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The research coordinator and PIs will be available to monitor the data and correct any discrepancies based on source documents if needed.

Data to be collected from each subject via chart review includes: demographics, relevant vital signs (including height, weight, waist circumference, and blood pressure),

obstetrical history, current medications, relevant laboratory results, and other pertinent information as relates to the research study.

For subjects enrolled in Intervention A or B, personal information that is recorded through the online resource will be available to the study team in a de-identified manner compliant to IRB policies. At the time of completion of the study, the principle investigator will receive an encrypted document from the X-PERT information technologist that will include the personal health information that the subjects entered into the application. This information will be provided with the subjects' study related email address which has already been de-identified. This information will be used in the data analysis of the study. Any information involving the online application will not be available to the researchers at the time of study visits.

For subjects enrolled in Intervention B, the X-PERT trained professional leading the group sessions will have access to the personal health information for the subjects' enrolled in their group sessions. The information will be transferred from the X-PERT information technologist to the X-PERT trained professional in an encrypted and de-identified manner. The X-PERT trained professional will not have direct personal health information about the individual participant, rather the X-PERT trained professional will receive data about the total subjects enrolled in the class. The data will be accessible to the professionals at the time of each group session through the completion of the 12-week course.

Health records will be reviewed from initiation of obstetric care through the 6- month postpartum period. Throughout the study period and up to 2 weeks after the final study visit, the principle investigator (PI), co-investigator, and research coordinators will review medical records for outcomes. The subject will be requested to sign a medical records release to obtain medical records if the patient receives care at a non UTMB hospital or clinic.

3.1. Study visits/Follow-up

Screening recruitment and consenting

Screening
Under the direction of the PI, trained research staff will be available to screen and consent subjects according to study protocol. Medical records of all potential subjects with a BMI ≥ 30 kg/m^2 (calculated by weight at the final prenatal visit prior to delivery) will be reviewed and those who satisfy inclusion and exclusion criteria will be approached at UTMB and a written informed consent will be obtained. A screening log will be used to track all subjects approached for the study.

The potential subjects that are recruited for the study will be contacted by the PI, co-investigators, or other trained research staff during their postpartum stay in the hospital. There will be no recruitment for the research study prior to birth. Research staff will review patients' electronic medical record. The health care provider of the

potential subjects will be notified that the patient may qualify for this research study. The health care provider will inquire if the patient would like to discuss the study with research personnel. If so, research staff will discuss the study with the patient and invite her to take part in the research study. Subjects will be recruited, enrolled and consented in a private room in order to respect the privacy of potential subjects.

Consenting process
Written consent will be obtained by direct person-to-person contact.. The PI, study coordinator, or a collaborator will be responsible for the informed consent. Subjects will be given time needed in order to fully understand and read the consent forms. All efforts will be made by the research staff to answer all questions the subject has and to ascertain that subjects have the right to refuse to participate in the study. As part of the consenting process, an assessment of comprehension and understanding of the English language will be performed. The potential subject will be given a sample of the X-PERT printed document. The potential subject will answer three questions about the sample material. Understanding and comprehension of the English language will be assessed by the research staff consenting the patient for the study. The potential subject will be required to answer all three questions correctly in order to be a potential candidate for the study.

Randomization
A confidential computer-generated simple randomization scheme will be prepared and provided on an ongoing basis to our study coordinator. A randomization log with group assignment, subject name and medical record number will be used to track the randomization process.

Group assignment/Intervention
Once a subject is consented and randomized, the appropriate intervention according to group assignment will be implemented.

Visit #1 at 2-3 weeks postpartum, Visit #2 at 3 months postpartum and Visit #3 at 6 months postpartum.

All patients will have a blood sample and urine sample collected at each study visit. The blood and urine sample will be collected while the patient is fasting. The fasting period is defined as at least 8 hours without food. The subjects will be allowed to drink water. All subjects will have the option of first morning visits in order to utilize the overnight period as the fasting period.

A standard 4oz sterile urine collection cup will be provided for each urine sample. Urine will be checked for glucose and ketones by dipstick. Approximately 20mL of blood will be collected at each study visit. The urine sample will be assessed for urine glucose and ketones by urine dipstick. The blood samples will be used for the following tests: Hemoglobin A1c (HgA1c), lipid panel, homeostatic Model Assessment (HOMA) test for insulin sensitivity or resistance. The samples will be taken to the lab and/or stored at -80^{0}C in our perinatal research department for later processing for use in the research study.

Subjects' vital signs, including blood pressure, waist circumference, height and weight, will also be recorded.

The data collected will not be used for clinical diagnosis or treatment purposes. Subjects will be reassured that participation in the study is voluntary and will not interfere with diagnosis or treatment of her condition.

3.2. Baseline Procedures

Routine postpartum care will be provided by the subjects' clinical providers. Trained and experienced research staff will be responsible for all research study procedures and data abstraction.

Several data collection forms will be used during these processes. Data on these forms, devoid of personal identifiers, will be securely stored at our perinatal research division.

3.3. Withdrawals

Subjects who become noncompliant will still be followed for outcomes. Noncompliant will be defined as missing one or more study visits. Additionally, if enrolled in Intervention B, noncompliant will be defined as missing six or more group sessions. Subjects who withdraw from the study after randomization will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in an intent to treat fashion. Those who withdraw prior to determining the primary outcome will be accounted for by randomizing an equal number of additional subjects.

3.4 Outcomes

Primary outcome:

Our primary outcome will be insulin sensitivity/resistance.

Secondary outcomes:

- Maternal weight gain: change from baseline body weight at 3 months and at 6 months
- Development of diabetes postpartum (based on a fasting plasma glucose test >99mg/dL or the 75-g, 2-hour OGTT > 199mg/dL)
    - Initiation (if newly diagnosed postpartum) or continuation/restarting (if had gestational diabetes and now diagnosed as diabetes mellitus) of insulin and/or oral medications
- Worsening blood pressure in the postpartum period
    - Blood pressure: ≥140/90 mm Hg or use of anti-hypertensive medication or increased dose of anti-hypertensive medication
- Other metabolic issues (e.g., thyroid disease, fatty liver disease etc.) discovered through chart review)

The primary outcome (insulin sensitivity/resistance) will be evaluated via the HOMA insulin sensitivity or resistance tests.

Secondary outcomes will be reviewed as follows:

1. Maternal weight gain: Change from baseline body weight at enrollment of study as compared to body weight at 3 month postpartum study visit and 6 month postpartum study visit.
2. Development of diabetes postpartum: As part of routine postpartum care, women at risk for development of diabetes postpartum are evaluated with a fasting plasma glucose test or 2 hour oral glucose tolerance tests. These tests are part of routine clinical care (when indicated) and will be accessed by the research staff through chart review.
3. Worsening blood pressure in the postpartum period: Blood pressure recorded at the time of enrollment to the blood pressure recorded at the 3 month postpartum study visit and 6 month postpartum study visit will be compared. The addition of an anti-hypertensive medication or increased dose of an anti-hypertensive medication will be accessed by the research staff through chart review.
4. Other metabolic issues, such as thyroid disease, fatty liver disease, etc: Additional metabolic issues will be reviewed by the research staff through chart review.

The PI will review and validate the diagnosis for all subjects identified to have the primary outcomes. These reviews will be conducted masked to treatment group. If there is uncertainty, a co-investigator will review the chart and discuss with the co-investigators as needed and make a final determination regarding the outcome.

4. Criteria for inclusion of subjects:

- Maternal age ≥ 18 years and <50 years
- Delivery at UTMB
- BMI ≥30 kilograms/meters^2 at the final prenatal visit prior to delivery
- Singleton gestation
- Accessibility to the internet
- A basic understanding and comprehension of the English language to be assessed by study personnel at the time of recruitment of the study.

  As part of the consenting process, an assessment of comprehension and understanding of the English language will be performed. The potential subject will be given a sample of the X-PERT printed document. The potential subject will provide written answers to three questions about the sample material. Understanding and comprehension of the English language will be assessed by the research staff consenting the patient for the study. The potential subject will be required to answer all three questions correctly in order to be a potential candidate for the study.

5. Criteria for exclusion of subjects:

- Enrolled in another trial that may affect outcome
- Subject who is unlikely to be followed-up after delivery

- Diabetes mellitus on medication; gestational diabetes requiring medication at the recruitment visit
- Other serious medical condition at the discretion of the PI (e.g., heart failure, kidney failure, severe asthma)
- Planned pregnancy during study period

6. Sources of research material

Electronic medical chart/records, blood samples, questionnaires.

7. Recruitment Methods and Consenting Process:

Please refer to section 3.1 above.

8. Potential risks:

8.1. Randomization Risk

Since the diet regimen will be randomized, it is possible that one or more of the other treatment groups will have more benefit than the group to which subject is assigned.

8.2. Loss of Confidentiality

Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

8.3 Blood Draw Risk

Each subject will have three blood draws collected throughout their participation in the study. Risks of taking a blood draw include pain, a bruise at the point where the blood is taken, redness and swelling of the vein, and infection. There is a rare risk of fainting.

8.4 Side effects of low carbohydrate diets (Intervention)

Subjects may experience minor side effects like headache, food cravings at the initiation of a new diet.

9. Subject Safety and Data Monitoring:

The collaborators and research coordinator will be responsible for monitoring the safety of this study. The report will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues. The collaborators and research coordinator will monitor for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries. Data collection will be identified with a participant ID number. Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database. Several data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The

research coordinator and PIs will be available to monitor the data and correct any discrepancies based on source documents if needed.

10. Procedures to Maintain Confidentiality:

Each subject will be assigned a study number with personally identifiable information deleted or removed. If needed, charts will be reviewed in the medical records area. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB password-protected computer in a locked room.

11. Potential benefits:

Obesity is an evolving epidemic and there is a strong association with consumption of an unhealthy diet. This study may show that the X-PERT program may lead to better maternal outcomes.

12. Statistical approach:

Analysis will be performed by intent to treat. Univariable and multivariable analysis will be used to describe the population in the study and to identify potential confounding variable. Standard normality analysis will be used. Demographics and descriptive statistics such as t test, Pearson's chi square, and Mann-Whitney tests will be used as indicated. Data will be either shown as median +/- IQR or mean +/- SDEV as appropriate.

Statistical analyses of primary and secondary outcomes between three groups will be performed by ANOVA or non-parametric equivalent. The statistical method used for power calculation is ANOVA. The sample size was calculated using a superiority trial design using HOMA IR as the primary outcome to measure the overall effect size across the three groups. Based on prior data published (18), we assume effect size of our intervention to be 25% in estimating the group mean of 1.4 , 1.05, and 1.05. Assuming within group variance of 0.8, our proposed sample size of 96 per group (total sample size of 288) will reach a power of 80% at alpha of 0.05. Above power calculation was performed by STATA 15.0.

Assuming ~10% loss to follow, this study proposes a total of 321 subjects will be needed to complete the study. This trial will be registered with Clinicaltrials.gov before recruitment is initiated and after IRB approval.

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