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Project title: Glucose Control in Type 2 Diabetes in Pregnancy

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1. Background:

Pregestational diabetes mellitus affects 1-2% of all pregnancies in the United States each year, and the incidence continues to increase at an accelerated rate. From 2016-2021, there was a 27% rate increase in women giving birth with pregestational diabetes [1]. In addition, there are racial disparities associated with pregestational diabetes, with the lowest rates in Caucasian women and the highest rates in Black, Native American, and Hispanic women [2].

Pregestational diabetes is also comprised of both Type 1 and Type 2 diabetes mellitus; however, these are the result of vastly different mechanisms. Similar to the pathophysiology of gestational diabetes in pregnancy, Type 2 diabetes is related to insulin resistance (as opposed to insulin deficiency in Type 1) and is closely associated with obesity and sedentary lifestyle. Because of the characteristics, Type 2 diabetes is likely to respond to lifestyle interventions for improvement.

Lifestyle modification is an important part of blood glucose management in pregnancy. Although the primary focus is typically diet modification, physical activity is also associated with improved glucose control [4–5]. Andersen et al. followed 14 women with diet-controlled gestational diabetes in Denmark and found reduced mean glucose in patients with 20 minutes of walking after each meal [6]. In addition, short periods of post-prandial walking were found to have similar effect on glucose concentrations compared to longer strenuous activity [7]. Outside of pregnancy, postprandial walking was found to be superior to pre-meal exercise for management of Type 2 diabetes [8].

Optimization of glucose levels in pregnancy can reduce the risk of several adverse outcomes, which include miscarriage, congenital birth defects, macrosomia, intrauterine fetal demise, and neonatal morbidity [2]. Traditionally in pregnancy, patients with diabetes would monitor blood glucose levels four times daily: fasting and then 1- or 2-hours postprandial. However, more recently, continuous glucose monitoring (CGM) has become more popular and readily available. In a cohort of patients using CGM, Bartal et al. found that the proportion of the time glucose levels where within what is considered acceptable range, referred to as time in range was associated with neonatal outcomes [3]. Specifically, patients whose time in range was below 70% had worse neonatal outcomes than those with time in range at or above 70%.

We hypothesize that post-prandial walking will improve time in range on continuous glucose monitoring, as well as maternal and neonatal outcomes in pregnant patients with Type 2 diabetes. As an initial step in testing this hypothesis, we will conduct a randomized controlled trial to limit bias in evaluating these hypotheses. A FitBit will be provided to both groups to assess adherence to the walking regimen.

Each year, approximately 400 pregnant women with Type 2 diabetes are followed at Eastern Virginia Medical School Maternal Fetal Medicine. This would be the first randomized-controlled trial focusing on post-prandial walking utilizing continuous glucose monitoring and FitBit data in this US patient population.

2. Specific aims:

Aim 1. To examine the effect of post-prandial walking on time in range on CGM in pregnant patients with Type 2 diabetes

3. Study design:

We propose a randomized controlled trial of women with singleton pregnancies who present with a diagnosis of pre-gestational Type 2 diabetes. The participants will be randomized to the intervention group (post-prandial walks + standard care) or control group (standard care alone which includes the usual counseling regarding activity) in a 1:1 ratio. The participant will be randomized by a number-generating

computer software after recruitment at the gestational diabetes education class. All participants will receive a continuous glucose monitor and basic model FitBit for use and data collection.

Inclusion criteria
- Singleton gestation
- Known diagnosis of Type 2 diabetes OR meets new diagnosis of Type 2 diabetes in the first trimester (up through 13 weeks and 6 days) [9]
- Age ≥18 and <50 years
- Gestational age <32 weeks 0 days gestation

Exclusion criteria
- Non-English as primary language.
- Inability to participate in 20 minutes of walking at a time
- Known or suspected fetal anomaly or aneuploidy
- Prisoners
- Management of diabetes outside of Eastern Virginia Medical School Maternal Fetal Medicine

Because we are a tertiary care center, some individuals may be seen at several different time points in the pregnancy at time of recruitment. All of these participants can be included for recruitment until 32 weeks 0 days gestation.

3.1 Postprandial walking:
Post-prandial walking group
Participants will be instructed to walk specifically for 20 minutes after each meal (breakfast, lunch, and dinner).

Control group
Participants will receive the usual counseling regarding physical activity, which does not include post-prandial walking.

Both groups
All participants will be encouraged to continue exercise per the U.S. Department of Health and Human Services Physical Activity Guidelines for Americans and the American College of Obstetricians and Gynecologists recommendations, which includes at least 150 minutes of moderate intensity aerobic activity per week during pregnancy. Given these recommendations, post-prandial walking is minimal risk to the patient and is an activity that patients may choose to do even outside of this study.
Both groups will have a fasting blood draw and urine sample at enrollment and between 34-36 weeks gestation in the outpatient setting, typically less than 25cc blood, to test for metabolomics.
Both groups will also have an estimation of body composition at enrollment and between 34-36 weeks gestation using bioelectrical impedance analysis (BIA), which introduces (non-invasively) a current into the body passing through a source electrode and a detector electrode, located on both hands and feet. BIA measures Resistance and Reactance and their vector relationship Impedance. Based on predictive equation, BIA estimates fat mass, fat-free mass, lean soft tissue, total body, intracellular, extracellular water, and phase angle. There are no known risks or discomforts related to the BIA. Minor discomfort is associated with the placement and removal of the electrodes on the skin.

4. Procedures:
4.1 Recruitment and Screening:
Subjects will be screened and offered recruitment if they meet inclusion and exclusion criteria. This will occur at the EVMS Maternal Fetal Medicine Diabetes Program Clinic. The length of active participation will be variable depending on when they enter our care, and our intervention will continue throughout pregnancy. Our primary outcome length will last 2 weeks, but from randomization to postpartum, it can be up to 37 weeks (almost the entire pregnancy). No direct involvement is needed from the patient after delivery. However, data collection for secondary outcomes via chart review will continue to be collected through 2 weeks postpartum.

4.2 Consenting process:

Patients will be approached at the EVMS Maternal Fetal Medicine Diabetes Program. The patients will be informed that the purpose of the study is to evaluate the effect of physical activity on glucose control and that all participants will receive a FitBit Inspire 3 and continuous glucose monitor (Dexcom G7). The patients will be informed that the groups will receive two different types of counseling regarding physical activity. A patient may be withdrawn from the study if a provider outside of the research team no longer deems that participation is in the best interest of the patient. Participation in this research study will not affect any other aspect of the patient's care. The patient may withdraw from the study at any point without affecting her care. No inducements will be offered to terminate a pregnancy. Those engaged in this study will not take any part in decisions regarding termination of pregnancy and if the patient desires termination or questions the viability of the pregnancy, the patient will be referred to a non-investigator for appropriate care.

Due to the risk of introducing bias when divulging the details of the intervention group procedures to the control group, authorized deception will be utilized during the consent process. A general overview of the study that focuses on standard of care will be provided to the patients initially. If the patient is randomized to the intervention group, they will be provided with a second consent form outlining the randomization to 20 minute postprandial walks. Two separate consent forms will therefore be used: one for all participants prior to randomization, and another for the intervention group only outlining the specifics of the postprandial walk intervention.

5. Randomization:
This will be a randomized-controlled trial 1:1. Randomization to each group will be conducted via the REDCap randomization module.

6. Outcomes:
Our primary outcome is the time in range (via CGM data) during the management of Type 2 diabetes in pregnancy between 34 and 36 weeks gestation. We chose this primary outcome because it is at the time of peak insulin resistance and time in range is more closely associated with pregnancy outcomes as compared to other means of monitoring glucose control.

Secondary outcomes include FitBit data (duration of postprandial walk (in minutes), sleep duration, baseline heart rate, maximal heart rate during walks, frequency of aerobic exercise per week), CGM data (mean glucose level, glucose excursions, fasting blood sugar), total daily insulin dose, fetal demise, fetal growth restriction, preeclampsia, placental abruption, mode of delivery (cesarean or vaginal delivery), indication of cesarean delivery, presence of shoulder dystocia (for vaginal deliveries), quantitative blood loss (QBL mL), postpartum hemorrhage (QBL > 1000 mL), infection (either chorioamnionitis or postpartum endometritis prior to discharge), birth weight (gram), APGAR scores, neonatal infection (defined as sepsis, fever, positive cultures, or a suspicious clinical course that warranted antibiotics treatment), respiratory distress syndrome, necrotizing enterocolitis, and neonatal intensive care unit admission (NICU), and days in NICU. Other secondary outcomes will include metabolomic markers collected from the urine and blood, as well as body composition data.

We will also collect demographic and clinical characteristics including maternal age, gestational age at delivery, race, ethnicity, insurance, marital status, history of preterm birth, parity, and number of previous cesarean or vaginal delivery.

Chart review for secondary outcomes and demographic/clinical characteristics will be completed through Allscripts, EPIC, and Powerchart.

7. Data Gathering and Safety:
The FitBits, continuous glucose monitors, and all supplies for the patient will be paid for with no cost to the patient or the patient's insurance company. The Marwan Ma'ayeh Discretionary Research Fund is covering the cost of the FitBits and CGMs. For the Dexcom G7, it is recommended that the sensor be changed every 7 days, which will be performed by the patient. Therefore, the sensor will need to be changed between 8 and 37 times throughout the study period, dependent upon what gestational age the patient was enrolled.

The research team will gather the data from the continuous glucose monitors via the share function, similar to how the data is shared to the clinical team.
The primary outcome will focus on the 34 through 36 week gestation data. However, the data from the rest of the subject's participation will be included in the secondary outcomes.
There will be two blood draws: at enrollment and again between 34 and 36 weeks gestation. A urine collection will also be performed at these times. These will be collected at an already scheduled clinic appointment. Therefore, no additional appointment will be needed for this. It will be drawn by phlebotomy staff or research nurses. It will be kept refrigerated, processed within 24 hours, and kept in -70 degree freezer in a secured area. After collection, samples will be run and kept in a separate repository for potential future use. This will be paid by the Marwan Ma'ayeh Discretionary Research Fund. There will be no cost to the patient.

The study dataset and ID key will be stored in REDCap in separate projects due to inclusion of data from the EMR.

8. Sample size calculation: Time in range in pregnant patients with pre-gestational diabetes is 66.3% with a standard deviation of 21.3% [3]. We assume that 20 minutes of postprandial walking after each meal will decrease the mean glucose by 30%. Therefore, assuming a 30% improvement in time in range, with a power of 80% and alpha of 0.05, 18 mother/neonate pairs per group would be needed to reach statistical significance. Assuming a 10% loss to follow up rate, a total of 40 mother/neonate pairs will be included in the study.

9. Statistical analysis: Descriptive statistics will be provided first for describing the subjects' demographic and clinical characteristics. Fisher's exact or Chi Squared test will be used to compare categorical variables and the Student t-test or Man-Whitney U test will be used to compare numerical variables.

References:

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