Title: Maternal continuous glucose monitoring surveillance compared to finger-stick glucose monitoring in pregnancies with type 2 pregestational diabetes

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RESEARCH PROTOCOL TEMPLATE
INVESTIGATOR INITIATED TREATMENT TRIALS

Title of Project: Maternal continuous glucose monitoring surveillance compared to finger-stick glucose monitoring in pregnancies with type 2 pregestational diabetes

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Abstract
About 1-2% of pregnant patients in the United States have pregestational type 2 diabetes (T2DM). The current standard of care for patients needing pharmacotherapy is to initiate basal and postprandial insulin as determined by patient's reported blood glucose levels after a week of finger-stick glucose monitoring (FSG). This approach is dependent on the patient performing four finger sticks daily and keeping a record of those values. Titration of medication is also dependent on this process. Patient adherence is reported at 50%. Continuous glucose monitors (CGMs) allow for continuous collection of blood glucose data without the patient needing to stick themselves or record their values. The goal of this randomized control trial is to determine if CGMs have greater adherence compared to FSG.

A. Specific Aims

Our first aim is to compare adherence to glucose monitoring using CGM vs. finger stick monitoring in pregnant patients with T2DM. Our second aim is to compare neonatal and maternal outcomes using CGM vs. finger stick monitoring in pregnant patients with T2DM. We hypothesize that CGMs will have increased adherence compared to finger stick glucose monitoring. We also hypothesize that CGM will lead to improved glycemic control, improved neonatal outcomes, and improved maternal outcomes compared to finger stick glucose monitoring

B. Background and Significance

Pregnancy is a state of insulin resistance to ensure that the growing fetus has ample nutrition. However, in patients where insulin resistance already exists, e.g., patients with T2DM, they have higher risks of pregnancy complications. They are at risk of having larger neonates, neonates with low sugar levels in the first 24 hours of life, higher rates of cesarean delivery, stillbirth, and hypertensive or high blood pressure disorders of pregnancy, such as preeclampsia[1,2]. Prior studies have demonstrated that treating elevated blood glucose can reduce these risks. However, patient adherence to FSG is reported at 50%[3]. There are no studies published on adherence to CGMs among patients with T2DM.

C. Preliminary Studies/Progress Report

The CONCEPTT trial demonstrated that continuous glucose monitoring (CGM) use in pregnancy for type 1 diabetics (T1DM) was associated with improved neonatal outcomes when compared to FSG[4]. However, for T2DM, there are minimal evidence of CGM use in this population. There have been no large clinical trials evaluating CGM use among T2DM. The current published literature is underpowered, and contradictory. Murphy, et al. showed improved glycemic control, reduced birthweight and reduced macrosomia[5], while Secher, et al. and Voormolen, et al. showed no difference[6,7]. Thus, there remains a dearth of literature to assess the utility of this glucose monitoring modality in T2DM.

D. Research Design and Methods

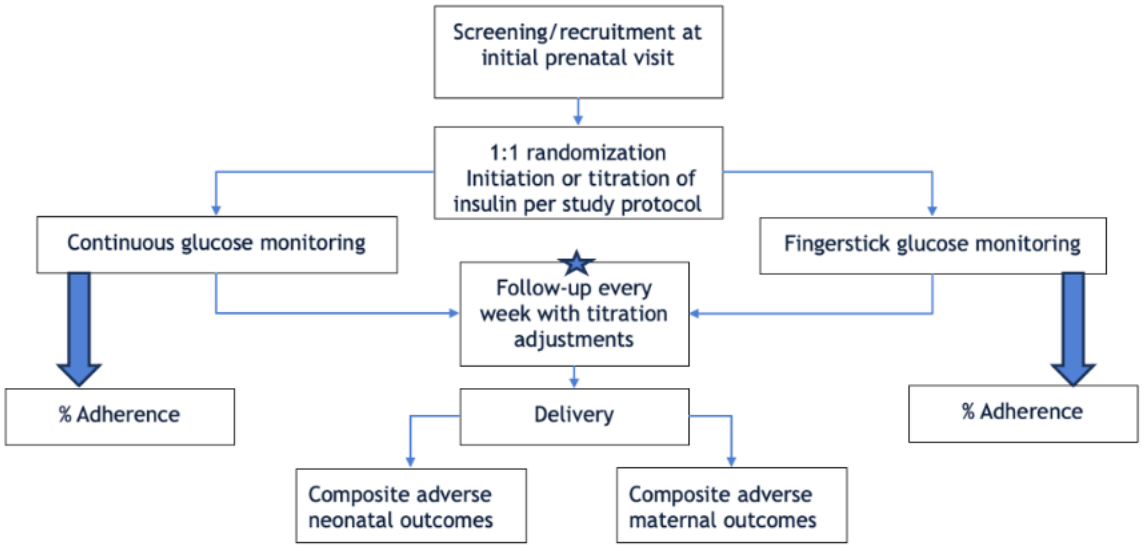
This is a prospective randomized controlled trial (RCT) comparing the rate of adverse neonatal and maternal outcomes between groups comparing CGM vs. FSG in patients with pregestational T2DM prior to initiating prenatal care. T2DM will be defined as the American Diabetes Association (ADA) criteria for diagnosis prior to the date of conception. Patients will receive a CGM after diagnosis will target blood glucose ranges between 65-140 mg/dL. Participants will be recruited at their initial prenatal visit for T2DM.

Participants will be screened, consented, and recruited at their initial prenatal visit. They will then be randomized to either the control FSG arm or the intervention CGM arm. Patients with T2DM are seen every 1 to 2 weeks for medication titration and BG checks, and we would continue this workflow, following patients to delivery. If the patient requires insulin uptitration, a weight-based regimen as described by the ADA will be used. Patients will be seen every 1-2 weeks to titrate insulin to meet target ranges. Percent adherence will be recorded in the medical record, which will be ear tagged in pinky sticky on EPIC by research personnel after enrollment and these patients will be seen by the same providers throughout their pregnancy. The only difference in management between two groups will be the way we measure blood glucose. Any indications for delivery will be managed in the same manner independent of group assignment based on the institution's clinical guidelines. After delivery, we would review the documented neonatal and maternal outcomes and documented adherence. Please see Figure 1 below for workflow.

The primary outcome is percent adherence, which will be calculated as number of days used with >75% of time coverage divided by the number of days from initiation to delivery for CGM and number of values reported divided by 28 (4 values are intended to be reported daily), divided by weeks from initiation to delivery for FSG. Secondary outcome is a composite of adverse neonatal outcomes, including the following measures: stillbirth, miscarriage, large for gestational age (LGA) of neonate defined as birth weight >90th percentile for gestational age, fetal hypoglycemia defined as glucose <40 mg/dL <48 hours after birth or glucose, hyperbilirubinemia, stillbirth or neonatal death, or birth trauma. Another secondary outcome is a composite of adverse maternal

outcomes, including the following measures: maternal hypoglycemia < 60 mg/dL, shoulder dystocia, OASIS Injuries, operative delivery or c-section, postpartum hemorrhage, or hypertensive disorder of pregnancy.

Figure 1. Study workflow



E. Statistical Methods

We will compare the percent adherence between the finger stick glucose and the continuous glucose monitoring group. We will need to recruit 70 patients to achieve a power of 0.80 for an effect size of 0.5 and alpha level of 0.05, anticipating 80% enrollment and 10% attrition from the study. Descriptive statistics will be performed to summarize continuous and categorical data. Continuous data will be tested for normality. Student's t test will be used to compare continuous data between groups if the data is normal and Wilcoxon rank sum test will be used to compare continuous data that is not normally distributed. Fisher exact test will be used to compare categorical data. Intention to treat analysis will be used for the primary outcome.

F. Gender/Minority/Pediatric Inclusion for Research

There will be no effort to recruit any particular racial or ethnic group. We expect our study population to reflect the patient population at large. Economically disadvantaged persons will be eligible to participate. Funding is provided in the study budget to pay for any needed medical evaluations for screening, for any patient who is not insured or has limited insurance coverage. Financial incentives for participation are reasonable to compensate for time, but not so large as to represent a coercive inducement to participation. Students and employees will be able to participate if referred via usual channels. No student or employee will be pressured to participate. Any student or employee wishing to participate will be explicitly told that a decision not to participate

will in no way affect their educational or employment status.

G. Human Subjects

There will be a total of 70 patients needed for the trial. Inclusion criteria include patients >18 years of age, singleton pregnancies, fetuses without anomalies, diagnosis of Type 2 diabetes, initiation of prenatal care at <20 weeks gestation. Among those meeting inclusion criteria, patients will be excluded for Type 1 diabetes, allergy to insulin, and inability to wear CGM. Research materials will be acquired in the form of patient data recorded in electronic medical records. Patients will be recruited and consented at their prenatal visit. Continuous glucose monitors are well-validated as alternatives to finger-stick glucose and have passed safety measures for their approval for use in diabetic patients by the FDA. The direct benefit that can be achieved by the continuous glucose monitor is increased adherence, and therefore improved insulin titration for the pregnant patient. Potential risks include subject difficulty in using the continuous glucose monitor (low likelihood).

H. Data and Safety Monitoring Plan

This protocol poses minimal risk. Only study investigators and personnel will have access to secure RedCAP database linking patient identifier with study ID. Due to the need to follow pregnancy outcome, it will be necessary to collect identifiable information such as name, date of birth, and medical record number. This information will be maintained on a separate secure RedCAP database linking patient identifiers with study IDs.

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