Once-Daily Versus Twice-Daily Insulin Glargine in the Management of Patients with Pregestational Diabetes Requiring Insulin

Protocol

Version II

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1. Introduction

1.1. Study Abstract

Insulin is the first-line medication for use to manage diabetes during pregnancy. Insulin analogs such as glargine have the advantage of a longer half-life allowing a steady basal insulin rate with less frequent drug administration to aid with blood sugar control. However, there is individual variation in the duration of action of insulin glargine in the non-pregnant population, and the pharmacokinetic changes in insulin glargine in pregnancy have not been studied. Data from non-pregnant people with Type II diabetes suggest that twice-daily dosing of insulin glargine may be more effective in blood glucose control than once-daily dosing.

This document describes a protocol of a randomized trial of once-daily versus twice-daily (in a split dose) insulin glargine use in pregnant patients with pre-gestational diabetes mellitus.

1.2. Study Hypothesis:

In pregnant patients with pre-gestational diabetes, twice daily insulin glargine use is associated with improved glucose control compared to once-daily dosing.

1.3. Purpose of the Study Protocol

This protocol describes the background, design and organization of the randomized clinical trial. Institutional Review Board (IRB) approval will be obtained prior to beginning recruitment.

2. Background

2.1. Introduction

Pregestational diabetes affects 1-2% of all pregnancies.[1] Maintaining blood sugar at physiological levels during pregnancy decreases the risk of hyperglycemia-induced adverse maternal and fetal outcomes. Adverse outcomes include spontaneous abortion, fetal anomalies, preeclampsia, preterm labor, stillbirth, congenital malformations, and more.[2]

Insulin glargine is an insulin analog that has an onset of action of 1-2 hours, a duration of action of 24 hours, and no peak action.[1] This has provided the benefits of ease of administration (with a once-daily dose) and providing a steady basal insulin level with no peaks and troughs.

However, there remains some controversy and limited evidence surrounding the optimal dosing strategy of insulin glargine. Studies in non-pregnant populations show more variability in the onset and duration of action of the medication than initially thought.[3–5] Additionally, data in patients with Type I and Type II diabetes outside pregnancy suggests improved glycemic control

with twice-daily dosing.[6,7]

Data in pregnant populations is lacking. Pregnancy is associated with changes in drug absorption, metabolism, elimination, and transport, which further add to the complexity of dosing of drugs such as insulin glargine in pregnancy.[8] Level 1 Evidence to guide optimal dosing strategies in pregnancy is not available. However, insulin glargine has been studied transplacentally, where it was established that in therapeutic concentrations, insulin glargine did not cross the placenta.[9]

2.2. Blood sugar monitoring

Technological advances have made continuous glucose monitoring (CGM) more practical to use to monitor pregnant patients, particularly those with pre-gestational diabetes. One variable that has been studied in relation to obstetric outcome is time-in-range for blood glucose on CGM (TIR). This is defined as the percentage of time in a day with blood glucose levels between 60-140 mg/dL. Studies suggest that a TIR of <70% is associated with neonatal NICU admission, longer length of stay, RDS, and IV glucose administration.[10] It is also associated with an increased incidence of hypertensive disorders of pregnancy.

However, the cutoff value of TIR greater than 70% is arbitrary, and there may be benefit in decreasing adverse maternal and neonatal outcomes with smaller difference in TIR. Additionally, the use of CGM might be a useful tool for pregnant women at risk for hypoglycemia.[2]

2.3. Rationale for Randomized Trial and Hypothesis

Insulin glargine has not been studied in randomized controlled trials involving pregnant women with diabetes.[2,9] Due to variability in the pharmacokinetics of glargine in the non-pregnant populations, and studies outside pregnancy suggesting improved glycemic control with twice-daily dosing, we hypothesize that the use of glargine twice a day will result in improved glycemic control when compared to a once-daily dose.

This study is designed to test the glycemic response to the 2 regimens in the third trimester of pregnancy, a period of heightened insulin resistance. If we find a difference in glycemic control, then we will plan a larger trial to evaluate the impact on a clinical outcome, such as neonatal outcome.

3. Study Design

3.1. Primary Research Question

This randomized trial will address the primary research question:

> In patients with pre-gestational diabetes, does taking a twice-daily dose (in a split dose) of glargine result in improved glycemic control when compared to once-daily dosing?

3.2. Secondary Research Questions

Secondary research questions that this study will address are whether in patients with pre-gestational diabetes, a twice-daily dose of glargine compared to a once-daily dose will decrease the risk of:

- Composite maternal morbidity and mortality;
- Neonatal morbidity and mortality, including neonatal hypoglycemia.

3.3. Design Summary

This study is a non-blinded prospective randomized trial of pregnant patients with a singleton pregnancy between 24 weeks 0 days and 28 weeks 0 days gestation, who have Type II diabetes mellitus and using a continuous glucose monitor for glycemic control. Participants will be randomized to either:

- Once-daily insulin glargine;
- Twice-daily insulin glargine in an equal split-dose.

3.4. Eligibility Criteria

3.4.1. Inclusion Criteria

- Patients older than 18 years of age;
- The patient is fluent in English, physically and mentally able to understand the informed consent, and is willing to participate in this study;
- Type II diabetes mellitus requiring insulin;
- The patient is between 24 weeks 0 days and 28 weeks 0 days of gestation at the time of enrollment. Gestational age will be determined by last menstrual period, confirmed with a first trimester ultrasound, per the recommended guidelines by the American College of Obstetricians and Gynecologists.
- Currently using or willing to use a clinically indicated continuous glucose monitor for glycemic management

3.4.2. Exclusion Criteria

- Known allergy or reaction to insulin glargine, or concurrent medical condition where the use of insulin glargine is contraindicated;
- Contraindication to CGM use, patient declines CGM use, or CGM not covered by patient's insurance;
- Concomitant use of other anti-diabetic medication (such as metformin); use of a short-acting insulin will not be considered an exclusion;

- Known or suspected fetal anomaly or aneuploidy;
- Prisoners;
- Ongoing prenatal care outside EVMS or planned delivery outside Sentara Norfolk General Hospital.

3.5. Informed Consent Criteria

Patients will be approached at the time of one of their prenatal visits between 24 weeks 0 days and 28 weeks 0 days to determine study eligibility.

Written informed consent will be obtained before enrollment into the study. A copy of the consent form will be provided to the patient.

3.6. Randomization Method

Patients will be randomized to either once-daily or twice-daily glargine use. Patients will be randomized in a 1:1 ratio using a computer-generated random sequence using REDCap.

4. Study Procedures

4.1. Screening for Eligibility and Consent

Patients will be identified by the study team through the EVMS Maternal-Fetal Medicine provider schedules. The study team will then approach eligible patients at the time of one of their prenatal visits between 24 weeks 0 days and 28 weeks 0 days to determine study eligibility.

If a patient agrees to participate, a member of the study team will engage in the process of informed consent with the patient and the patient will sign the consent form.

4.2. Randomization

Patients will be randomized to taking either once-daily or twice-daily insulin glargine. The medication will continue to be prescribed to the patient's preferred pharmacy. This is typically covered by insurance carriers for patients with diabetes in pregnancy. If not covered under their insurance, the patient will be responsible for the cost of the prescription.

4.3. Baseline Procedures

The patient's eligibility information will be collected, including gestational age and estimated date of delivery, in addition to the following:

- Demographics: age, race, insurance status;
- Medical history: pre-pregnancy weight, current weight, height, current blood pressure, past medical history, diabetes history, history of diabetic ketoacidosis, last Hemoglobin A1c level;
- Social history: marital status, years of education, alcohol use, tobacco use, and other

maternal drug use;
- Obstetrical history: previous miscarriages and terminations, history of preeclampsia or other obstetric complications in prior pregnancies.

At the time of enrollment if the patient does not have one, they will be asked to wear a continuous glucose monitoring device for which they will get teaching on use and troubleshooting and be instructed to wear for the duration of the study.

There will be no preference for which CGM device the patient will be prescribed, and if one device is preferentially covered by the patient's insurance carrier then that CGM device will be used. This will be prescribed to the patient's pharmacy and billed to the patient's insurance. If the patient does not have insurance, or if the insurance does not cover the CGM, the patient will be responsible for the cost of the CGM. The patient's CGM will be prescribed up until the patient is 12 weeks postpartum, or until the patient transfers diabetes care to an endocrinologist, whichever occurs first.

Patients will be randomized to once-daily or twice-daily insulin glargine use.

- Patients already on insulin glargine once-daily who are randomized to the once-daily use group will be instructed to continue their current dose
- Patients already on insulin glargine once-daily who are randomized to the twice-daily use group will be instructed to split their dose, and take 50% of the dose in the morning and 50% at bedtime
- Patients already on insulin glargine twice-daily who are randomized to the once-daily use group will be instructed to take the entire dose once daily.
- Patients not already on insulin will be started on a total insulin dose of 0.5 u/kg/day, divided to 50% basal glargine (either once-daily or twice-daily according to randomized group) and 50% short-acting bolus insulin (divided into 3 mealtime doses).[11] Patients will be initiated at a reduced insulin dose to their weight-based regimen value (1.0 U/kg/day in the second trimester) to avoid hypoglycemia.[11]
- Patients on a long-acting or intermediate-acting insulin other than insulin glargine will be switched to insulin glargine to be taken once or twice daily according to their randomization group

The dose selected aligns with recommendations by the ADA and ACOG. Any further dose titrations or adjustments are not dictated by the study and will be at the discretion of the patient's clinical team. This is a pragmatic study and diabetes management will be at the discretion of the patient's provider.

The primary outcome will be measured as mean TIR from Day 7 to Day 14 after starting study

insulin dose.

4.4. Patient Management and Follow Up

Patients will continue to receive standard prenatal care with their treating physician. Patients typically have their blood pressure and weight measured at all prenatal visits, and this information will be collected.

Blood glucose will be reviewed weekly by email and phone, and insulin doses titrated to achieve a blood glucose target of 60 - 140mg/dL. Patient CGMs will be connected for electronic access by the study staff for review.

Study personnel will meet with participants monthly, at the time of prenatal care visits, to ascertain compliance with study agent, query for side effects or complications, and to chart abstract medical/obstetrical complications, recorded blood pressure, and hemoglobin A1c levels.

All other obstetric care is at the discretion of the primary provider, including but not limited to: treatment of maternal medical comorbidities or obstetric complications, timing and frequency of antenatal ultrasound, maternal and fetal surveillance, and timing and mode of delivery.
The study team will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy. Individuals engaged in the research will have no part in determining the viability of a neonate. If the participant requires either of these, a referral will be made to another clinician for such decisions.

4.5. Procedures in the Third Trimester, on Labor and Delivery, and Postpartum

At delivery, study personnel will chart abstract maternal and infant delivery information and maternal and infant data will be collected until day of discharge or up to 30 days postpartum, whichever occurs first. The data for this study will be collected from the Sentara EPIC and VHS EPIC electronic medical record.

4.6. Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol. Adverse events will be reported to the Institutional Review Board per policy.

4.7. Study Outcome Measures

4.7.1. Primary Outcome

The primary outcome is glycemic control. This will be evaluated using mean TIR between Day 7 and Day 14 after study enrollment.

4.7.2. Maternal Secondary Outcomes

- Hypertensive disorders of pregnancy
- Preterm birth < 34 weeks and <37 weeks, both spontaneous and indicated;
- Operative vaginal delivery and cesarean delivery;
- Estimated and quantitative blood loss;
- Blood transfusion;
- Maternal morbidity and adverse maternal outcomes, including endometritis / chorioamnionitis, wound infection, venous thromboembolism, massive transfusion and postpartum hemorrhage, ICU admission, and maternal death.

4.7.3. Neonatal Secondary Outcomes

- Antepartum, intrapartum, or neonatal death;
- Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiopulmonary resuscitation within first 72 hours;
- Hypoglycemia (glucose < 35 mg/dl) requiring IV glucose therapy;
- Birth weight;
- Neonatal encephalopathy as defined by the NICHD Neonatal Research Network criteria;
- Seizures;
- Shoulder dystocia;
- Birth trauma (bone fractures, brachial plexus palsy, other neurologic injury, retinal hemorrhage, or facial nerve palsy);
- Intracranial hemorrhage (intraventricular hemorrhage, subgaleal hematoma, subdural hematoma, or subarachnoid hematoma)
- Hyperbilirubinemia requiring phototherapy or exchange transfusion
- NICU admission

5. Statistical Considerations

5.1. Data Relevant to the Primary Outcome

Data from a prior study suggests that mean TIR in patients with Type I and Type II diabetes in pregnancy is 66.3% with a standard deviation of 21.3%.[10]

5.2. Sample Size and Power

To determine the appropriate sample size for our study, we employed a Bayesian simulation-based approach using Stata's bayesmh command. The primary outcome variable was modeled as a normally distributed continuous variable, with separate distributions for the control and

intervention groups. We assumed that the control group had a mean outcome of 0.663 (SD = 0.213), while the intervention group had a mean outcome of 0.762 (SD = 0.213), representing the expected treatment effect.

First, a wider range of samples to narrow down the range between 20 and 500 was used. Based on the results, we narrowed down simulation size to a range of sample sizes from 150 to 200 participants to evaluate the impact of sample size on the estimation of the treatment effect.

For each sample size, we fit a Bayesian hierarchical model with a normal likelihood and weakly informative priors: a normal(0,1) prior for the group effect and an inversegamma(2,1) prior for the variance parameter. The model was run with two Markov Chain Monte Carlo (MCMC) chains, a burn-in period of 5,000 iterations, and 10,000 post-burn-in samples to ensure convergence. Posterior estimates of the treatment effect, including the mean difference between groups and 95% credible intervals (CrI), were extracted and summarized.

The results indicated that, across all sample sizes, the posterior mean difference between groups consistently estimated the expected treatment effect, with credible intervals excluding zero for sufficiently large samples. For example, at n = 200, the posterior mean difference was approximately 0.075, with a 95% CrI of (0.007, 0.140), suggesting strong evidence of an intervention effect. At n = 195, the posterior mean difference was approximately 0.062, with a 95% CrI of -0.004, 0.129) suggesting that a larger sample size than 195 will be more appropriate. At a sample size of 196, the posterior mean difference did not cross zero (mean difference = 0.070; 95%CrI = 0.002, 0.139).

These findings support our proposed sample size range of 200 and provide robust Bayesian evidence for detecting meaningful differences between study groups.

5.3. Planned Analyses

Continuous variables will be analyzed using Student's t-test or Mann-Whitney-U test as appropriate. Categorical variables will be compared using Chi-squared or Fisher's exact tests as appropriate.

6. Data collection and security

Data collection will be done using REDCap database. Only individuals who are included as investigators or study personnel will be granted access to the database. The main REDCap database will NOT include any protected health information; patients will be identified by a unique Study ID. There will be a separate secure database at linking Study ID with the patient's MRN. User access will be granted by the PI only to IRB-approved site personnel. When study personnel/investigators are no longer part of the institution or study, the PI will be notified and their access to the database will be immediately discontinued.

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