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INVESTIGATOR-SPONSORED STUDY

The Use of Real-Time Continuous Glucose Monitoring (RT-CGM) in Gestational Diabetes

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RESEARCH PROTOCOL

TITLE: A Study on the Use of Real-Time Continuous Glucose Monitoring (RT-CGM) in Gestational Diabetes

A. Specific Aims/ Hypothesis: We hypothesize that use RT-CGM in those with gestational diabetes will improve/ reduce glycemic variability in pregnancy and potentially improve fetal and maternal outcomes.

Aim 1.Evaluate if Real Time Continuous Glucose Monitoring improves mean glucose, time in range, time above and below range, mean amplitude of glycemic excursions (MAGES) and standard deviation of blood sugars and coefficient of variation (CV)
Aim 2.Evaluate if improved glycemic variability improves fetal and maternal outcomes in pregnancies affected by gestational diabetes.
Aim 3: Evaluate participants' perception of RT-CGM use in pregnancies affected by gestational diabetes.
Aim 4: Evaluate nutritional and lifestyle changes in GDM and pregnancy and effect of RT-CGM
Aim 5: Evaluate if RT-CGM decreases need for initiation of oral diabetes medication and/or insulin. If insulin initiated, evaluate if RT-CGM reduces cumulative insulin dose.
Aim 6: Evaluate nocturnal hypoglycemia in pregnancy and if RT- CGM lessens nocturnal hypoglycemia

B. Background and Significance

Use of continuous glucose monitoring (CGM) has increased given improved sensor accuracy, greater convenience and ease of use, and expanding reimbursement. However, utilization of CGM technology in clinical practice, especially in gestational diabetes, remains low given paucity of clinical data. In February 2019, the Advanced Technologies & Treatments for Diabetes Congress convened an international expert panel to discuss this issue but because of the lack of evidence for CGM targets for women with gestational diabetes mellitus (GDM), percentages of time spent in range, below range, and above range were not included (1). Currently data are limited and studies are needed to show efficacy of this technology and thus we are conducting a pilot study of CGM in gestational diabetes in order evaluate maternal and fetal outcomes in the setting of CGM use in gestational diabetes.

C. Preliminary Studies

Many studies have demonstrated that RT-CGM can be used in adults and children with both Type 1 and Type 2 diabetes resulting in improvement in HbA1c and/or a reduced frequency of hypoglycemia (2-4). Our initial research showed that the use of RT-CGM serially over 3 months improved HbA1c by an average of 1.0% in subjects with Type 2 diabetes on no prandial insulin (5). Nutrition and activity changes were not measured but the 3-month HbA1c improvement was sustained for another 9 months without further RT-CGM intervention (6) but otherwise data is limited in type 2 diabetes and CGM use. Similarly, data in GDM and CGM use is limited: The largest study on GDM did show that standard deviation of blood glucose, mean amplitude of glycemic excursion (MAGEs) , and mean of daily differences values were significantly lower in the CGM group compared with those in the routine care group ($P < .001$) (7). A more recent study which reviewed

correlation between third trimester glycemic variability in non-insulin-dependent gestational diabetes mellitus failed to show any adverse pregnancy and fetal outcomes but did not report mean glucose (8). One recent study highlights that even more stringent targets may be needed (9) and another the importance of CGM mean glucose and time in range especially overnight (10) where data from traditional fingersticks is not typically available.

D. Research Recruitment and Population

A maximum number of 130 participants will be recruited that meet inclusion/exclusion criteria for the study. Dropouts will be replaced on a one-to-one basis as needed to reach a total of 95 completed/evaluable participants. Recruitment information about the study will be made available to all obstetrics and gynecological medical personnel including medical assistants, nursing staff, and physician and physician extenders at the University of Washington and associated obstetric sites by medical staff announcements and provider flier (Appendix F). Information about the study will be made available to patients by a study flier (Appendix H) which will provide contact information for the study coordinator. If potential participants express interest in the study to medical staff, permission for the study coordinator to contact them via telephone or email will be requested and potential participants will be contacted for further screening and potential enrollment. A HIPAA Partial Waiver of Research Subject Authorization Request (HRP-281) will be requested if needed so that the study coordinator(s) can pre-screen provider's clinics and approach potential eligible subjects at the time of their visit. This may also be used to complete a database search to identify potential eligible subjects ahead of a clinic visit that have elevated A1c or positive oral glucose tolerance test.

Subjects may also be identified through posters and flyers placed in the community, as well as through all University of Washington clinics and in the broader community through websites and other advertisements. Potential subjects who satisfy the study criteria and express interest in the study will be given information about participation either by mail, email or a phone call. Eligibility questions will be asked but no study related procedure will be performed until informed consent/authorization has been obtained (see Appendix C).

Please note that pre-screening questions are done prior to consent then once the participant has signed consents further screening will be completed.

The initial contact with the potential participant is a call to ask the participant if they would like more information about the study after the study has been introduced by their provider. If they say yes, a brief explanation about the study is provided. They are asked if they have questions and are asked if they would to receive a copy of the consent as an informational packet that they can discuss with family members and their caregiver. They are then asked if we can call them in follow -up after they receive the consent.

The study screening and research procedures will take place at the University of Washington Maternal Infant Care Clinic and other ancillary OB and neighborhood clinic sites of the University of Washington including: Northwest and Montlake Campuses, local Neighborhood clinics, as well remote clinics (Arlington and Yakima OB Clinics). If possible, the visit will be performed in person, but, given the increase in telehealth visits during

the COVID pandemic, if a potential participant is unable to couple the screening visit and/or research visits with standard OB appointments, then televisits for the research visits will be offered.

Population:

We propose to perform an observational prospective study that will involve 100 subjects with confirmed gestational diabetes. There will be 50 participants in the CGM intervention group and 50 in control group. Patients with pre-existing type 1 or type 2 diabetes will be excluded as will overt diabetes (Hba1c >6.5) on initial gestational diabetes screening and/or POC Hba1c. Gestational diabetes screening by oral glucose tolerance test and/ or HbA1c is performed in the OB clinic at initial early prenatal visit or 24-28 weeks based on patient risk. If positive, potential participants will be offered enrollment in the study. Currently the OB department estimates approximately 1400 deliveries annually at Montlake campus and 1100 at our NW campus. This would provide for approximately 2500 pregnancies in one year, with an anticipated 25 pregnancies with gestational diabetes per month. We will have robust population to recruit from. We do not see recruitment as an issue. We will also extend our recruitment to the Arlington and Yakima consult clinics, which see patients from the surrounding areas to increase diversity of our population as for example Seattle's demographics is 11% Hispanic while Yakima is 43%.

E. Statistical Considerations

Sample Size Estimation

The HbA1C outcome was used for the sample size calculation. Since we are collecting HbA1C every 8 weeks, we are able to leverage the repeated measures design in the estimation of the sample size needed for this study. This allows us to gain efficiency and reduce the number of subjects needed. Thus, for an effect size 'f' of 0.14, which is between small (0.10) and medium (0.25), an alpha of 0.05 and power of 0.80, we need a total of 92 study subjects. Allowing for some attrition in study subjects, we are planning to enroll 100 patients.

Note that this type of sample estimation requires that we specify the variance across observations (sphericity) and the correlation across observations. We specified both at 0.60. We calculated sample size using G*Power.

Data Analysis Plan

The data analysis will start with completion of the **CONSORT** diagram, with an analysis of differences between those who completed the study and those who did not (t-tests and chi-square tests, as needed, comparing basic demographics and baseline health characteristics), so that the researchers in this area can understand the extent to which our study contains bias.

Next, we will calculate summary statistics (means, medians, proportions, etc.) of all baseline measurements, overall and by study arm, so that we can fully characterize the study cohort.

Using the CGM data, we will graph each participant's trajectories over time and review each, examining for major patterns in the trajectories. Note that typically statistical analyses emphasize homogeneity in the data; however, this approach will allow for understanding of heterogeneity. As part of this examination of the CGM data, the analysis will calculate each participant's measures of glycemic variability (such as mean amplitude of glycemic excursions, coefficient of variation, etc.), HbA1C values, and fructosamine values and overlay them on each graph. This part of the analysis is predominantly exploratory.

For the statistical, hypothesis-testing examinations of HbA1C, fructosamine, CGM readings, and glycemic variability across key time points, we will conduct mixed models (i.e., multilevel model) analyses, which will allow us to quantify within-between interactions, or changes within subjects over time and differences across groups. These models can also include multiple independent variables/covariates.

F. Inclusion/Exclusion Criteria

Inclusion criteria:

1. Pregnancy and Gestation ≤ 30 weeks
2. Singleton pregnancy
3. Confirmed GDM (by 75g or 100g oral glucose tolerance test or HbA1c)
4. Able to read English
5. Is able to read, understand, and sign the Informed Consent Form (ICF) and if applicable, an Authorization to Use and Disclose Protected Health Information form (consistent with Health Insurance Portability and Accountability Act of 1996 [HIPAA] legislation), communicate with the investigator, and understand and comply with protocol requirements

Exclusion criteria:

1. Pre-gestational Type 1 or Type 2 diabetes.
2. Newly diagnosed overt-diabetes in pregnancy [HbA1c ≥ 48 mmol/mol (6.5%), fasting glucose ≥ 7.0 mmol/l, random glucose ≥ 11.1 mmol/l].
3. Pregnancies with established fetal anomalies (aside from echogenic intracardiac foci and/or renal pyelectasis) or possible preterm delivery secondary to maternal disease besides GDM
4. Known endogenous/exogenous Cushing's syndrome
5. Known chronic infections
6. Current use of any oral form of steroid medication
7. Already receiving continuous glucose monitoring (CGM)
8. History of bariatric surgery
9. Gestational Age less than 14 weeks

G. Diagnosis of GDM:

Per UW protocol and based upon the ACOG Practice Bulletin on gestational diabetes early screening for GDM prior to 20 weeks is recommended, preferentially in the first trimester in those at high risk especially in the overweight or obese (BMI ≥25 or ≥23 for Asian**)**

Screening Strategy for Detecting Pregestational Diabetes or Early Gestational Diabetes Mellitus (consider testing in all overweight/obese women (i.e. BMI ≥25 or ≥23 for Asian Americans) with one of more of the following risk factors:

Physical inactivity
First-degree relative with diabetes
High-risk race or ethnicity (African American, Latino, Native American, Asian Americans, Pacific Islander)
Prior infant weighing ≥4000g (~9lbs)
Previous GDM
Hypertension (140/90 mmHg or on therapy for hypertension)
High-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L),
Triglyceride level >250 mg/dL (2.82 mmol/L)
Polycystic ovarian syndrome
Hemoglobin A1C ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
Other clinical conditions associated with insulin resistance (ex: pre-pregnancy BMI ≥40, acanthosis nigricans)
History of cardiovascular disease

Early Screening & Diagnosis of GDM:

Screening may include early HbA1C in the above higher risk population. Per UW protocol interpretation of HbA1C will be:
-HbA1C ≥ 6.5% is diagnostic of pre-gestational DM. Diabetes education and therapy should be initiated as soon as possible and given pre-gestational DM will be excluded from the study
-HbA1C 6.0-6.4% may be considered diagnostic of GDM but confirmation testing with 3 hour glucose tolerance test is still considered standard of care. OB providers will ask patients to complete the 3 hour GTT. However, given potential exposure in 3-hour testing during the COVID-19 pandemic if patients decline then HbA1C ≥ 6.0% will be used for enrollment
-HbA1c 5.7-5.9% should be considered concerning for impaired glucose tolerance. Local protocol is re-evaluation for GDM with a 3 hour GTT at 24-28 weeks. In this case, the 1 hour GCT is not recommended as the initial screen as these women have already been identified as being at elevated risk for GDM. If patients decline 3-hour testing and elect for HbA1c instead, then HbA1C ≥ 6.0% may be used for enrollment.
-HbA1c <5.7% is normal; these women will have routine GDM screening at 24-28 weeks

Routine Screening & Diagnosis of GDM

We will use the 2 step protocol with oral glucose tolerance testing for diagnosis. For the glucola (50g) we will use a 1-hour cutoff of >140 or HbA1C ≥ 6.0% followed by the 3 hour for confirmation of GDM per local protocol at UW.

A 1-hour GCT level of 180mg/dl will be considered diagnostic of GDM without proceeding to a 3-hour GTT. In select situations based on either clinician's assessment or patient's refusal to accept diagnosis based on the

GCT, a 3-hour GTT may be considered for GCT results between 180-200mg/dL. A follow up 3-hour GTT is not required for any patient with a GCT ≥200mg/dL, as that value is sufficient for the diagnosis of GDM.

If the patient has an elevated glucola then the 100-g 3-hour GTT should be performed. This will include a fasting blood sugar, and a 1, 2, and 3-hour post GTT plasma glucose levels will be measured. The diagnosis of GDM is based if at least two of the four plasma glucose levels are met of exceeded using the Carpenter/Coustan criteria as outlined by the ADA (reference). The values are fasting 95 mg/dL (5.3 mmol/L), 1-hr 180 mg/dL (10.0 mmol/L), 2-hour 155 mg/dL (8.6 mmol/L), and 3-hour 140 mg/dL (7.8 mmol/L).

American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S14–S31(11)

H. Study Design

Study Design: Interested volunteers will be screened by telephone or in person in respective clinics or via televisit and then scheduled for a screening visit (week 0). If potential participants express interest, they will be provided an email address or phone number to call for more information. Alternatively, participants will be asked if they would like to be called to receive more information and are willing to provide their contact information to study staff. If after receiving more information, the potential participant is interested, then pre-screening questions (appendix D) will be asked. If still eligible, then a screening appointment will be arranged by study staff. If the participant is not interested in participating the participant will continue standard OB care for gestational diabetes.

Study visits and intervention: Upon arriving to the pre-intervention visit, informed consent will be obtained after which a point of care HbA1c (if no HbA1c available within the last 2 weeks) will be obtained and oral glucose tolerance test (OGTT) and or HbA1c results reviewed and inclusion/exclusion criteria reviewed. At the pre-intervention session (week 0) the control group will wear CGM for 10 days blinded. The intervention group will be given CGM training and instructions and start Real Time-CGM (RT-CGM). Controls will be asked to follow their OB provider's instructions for checking blood sugar via capillary blood glucose (ie fingersticks). If no recommendations have been given, instructions will be to start checking fingersticks fasting and 1-hour post-meals, which is typical for GDM management. All participants will be asked to write their glucose levels/results in a log provided. RT-CGM participants will be asked to review their RT-CGM and write down their fasting glucose in am, prior to each meal and 1 and 2 hours post-meal. As well they will be instructed to document any sugars <60mg/dl seen by CGM in their log.

Participants will then follow-up at week 2 (session 2) at which time the control group will have their blinded CGM data collected and the RT-CGM group will download their CGM data and ensure CGM working appropriately. The control group will continue to monitor fingerstick blood glucose as recommended by their

pregnancy obstetric provider. The intervention group will continue the RT-CGM device and will be instructed to continue fingersticks only when concerned for hypoglycemia and/or inaccuracy of sensor. The control and intervention groups will follow-up serially for the duration of pregnancy (see schematic for visits below). The control group will wear the blinded CGM at serial timepoints throughout pregnancy and the intervention group will have serial download of RT- CGM. Participants will also have labs checked every 8 weeks which will include HbA1C and fructosamine at beginning and end of the study. It is estimated that participants will be enrolled at 24-28 weeks and have 4 visits (estimating a pregnancy duration of 40 weeks). Some participants may receive a diagnosis of gestational diabetes earlier and thus have more sessions. Maternal and neonatal outcomes will be abstracted from delivery records.

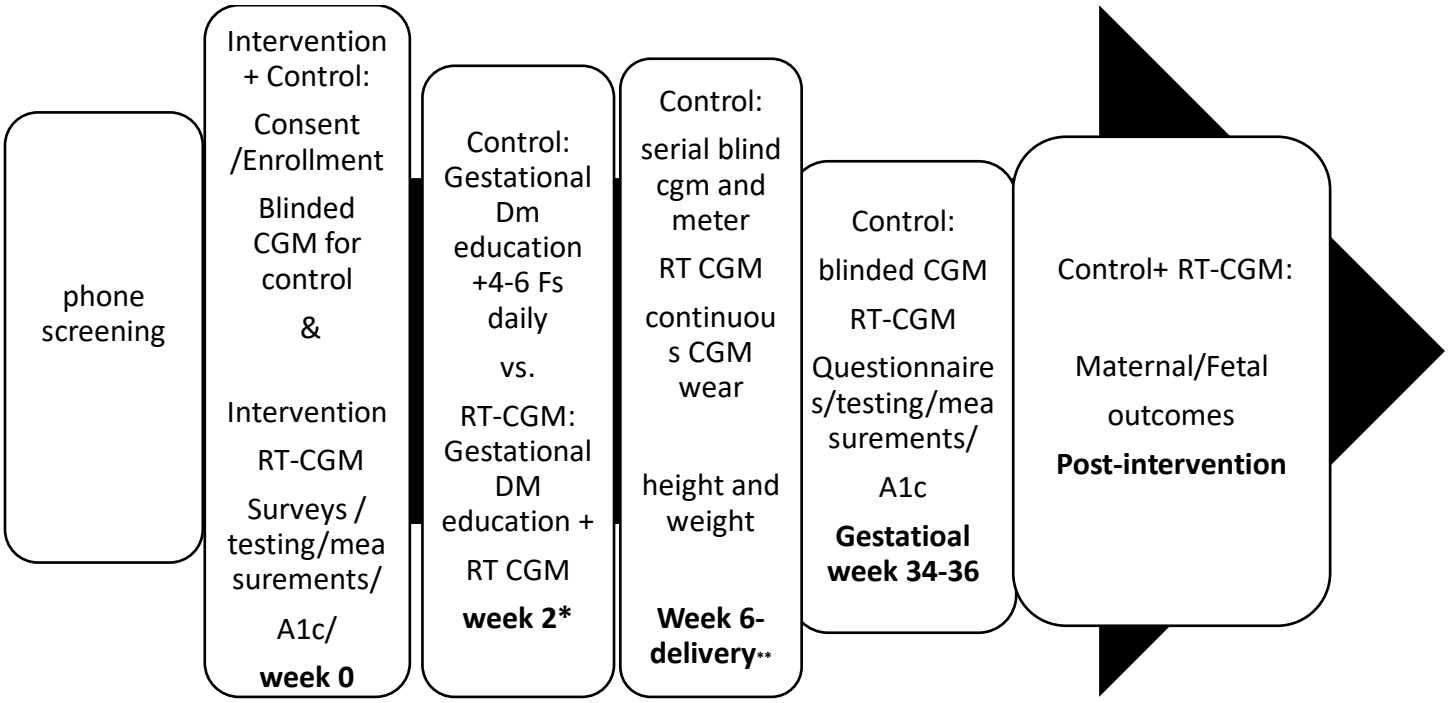

Figure 1: Study Design Schematic: N=100 Control N=50 GDM Intevention: GDM N=50
***Approximate Total duration of CGM use would be 14-22**
****see timeline for measurents appendix B**

Figure 2: Timeline for Visits Based on High Risk for Gestational Diabetes and Typical Risk

		Screening Visit 0	Visit 1b High risk	Visit 1a	Visit 2++	Visit 3	Visit 4*
Gestational age Intervention	High Risk	14	20-22 weeks	24-30 weeks	30-32 weeks	34-36 weeks	38-40 Weeks

Gestational age Intervention	Typical Risk	24-28	N/A	24-30 weeks	30-32 weeks	34-36	38-40 Weeks
Gestational age Control	High Risk	14	14-16 weeks	24-30 weeks	30-32	34-36	38-40 Weeks
Gestational age Control	Typical Risk	24-28	N/A	24-30 weeks	30-32 weeks	34-36	38-40 weeks

+++ visits will be a minimumof 2 weeks apart

*38-40 week data only collected in participants that make it to 38- 40 week gestational age

Screening/Pre-Intervention Visit(week 0):

Consent (appendix R) will be obtained prior to any screening procedures being completed, and conducted in a quiet room or private televisit. Participant will be given ample time to ask questions, and a copy of the signed consent form will be given prior to start of screening visit. Participants will fill out a contact form, including emergency contact. Study staff will review medical history and medications, pregnancy history, patient's mother's pregnancy history, sleep history, and lipid profile if available (appendix D), as well as all inclusion/exclusion criteria.

Vital signs will be collected, including height, weight (current and pre-pregnancy), blood pressure, maternal resting heart rate, and estimated gestational age. Maternal ultrasound results will be reviewed if available.

Glucose tolerence test results will be reviewed. Two blood pressure and pulse readings will be taken and HbA1c, both point of care (fingerstrick) and HbA1c serum and fructosamine via LabCorp will be obtained. Approximately 1 teaspoon of blood will be drawn. If a patient has an HbA1c documented in the medical record within 2 weeks of the pre-intervention session, then the point of care HbA1c will not be done. The available HA1c will be used. If they meet all inclusion and exclusion criteria (as outlined above), they will be randomized into either the RT-CGM intervention or control arm at the screening visit.

At the pre-intervention session (week 0) the control GDM group will be asked to wear the CGM blinded for 10 days. They will be asked to continue their usual diet and activity. If, for any reason, the CGM device fails to capture at least 3 days worth of data, the subject may be asked to repeat this measurement at an unscheduled visit. The control group with be given a glucose meter (onetouch) and instructed to follow their obstetric provider's recommendations about checking glucose by meter or if they have not been given instructions or do not remember their instructions they will be asked to check sugars fasting and 1 hour after meals. They will also be given a a handout that explains glucose goals and how food and activity effects glucose levels. (Appendix A1,A2). The intervention group will be given RT-CGM and instructed on use with a handout that explains glucose goals and how food and activity effects glucose levels (see handout/Appendix A). The intervention group will also be given a glucose meter (onetouch) and instructed to use for symptoms of low glucose or if they question the accuracy of the CGM. Both groups with be given standard gestational diabetes teaching and nutrition counseling by the RN in clinic and with individual nutrition appointments with the nutritionist, as per current local standard of care.

Participants will be given self-report questionnaires on physical activity, nutrition, sleep history, pregnancy history and overall wellness. Week 0 consenting and baseline data/measurements will take between 1 hour 30 minutes and 2 hours.

Week 2 (Visit 1a): Gestational Age 14-16 (Early GDM Dx) or 24-28 weeks (Regular GDM Dx)
RT-CGM and meter will be downloaded for intervention group and meter downloaded for the control group. Glucose logs will be collected. All participants will confirm they have completed RN gestational DM education and nutrition appointments per local standard of care. Vital signs, weight and medications and dose will be recorded at each visit and maternal ultrasound results if available (appendix M).

Week 6 (Visit 1b): Gestational Age 20-22 weeks (Early GDM Dx)
RT-CGM and meter will be downloaded for the intervention group and meter downloaded for the control group. Vital signs, weight and medications and dose will be recorded at each visit and maternal ultrasound results if available (appendix M).

Week 6/Week 14 (Visit 2): Gestational Age 30-32 weeks (Both Early GDM Dx and Regular GDM Dx)
RT-CGM and meter will be downloaded for the intervention group and meter downloaded for the control group. Vital signs, weight and medications and dose will be recorded at each visit and maternal ultrasound results if available (appendix M)

The control group will wear blinded CGM for 10 days and return during regularly scheduled OB visit. The study staff will follow up with participants to remind them to return the devices. If for any reason, the CGM device fails to capture at least 3 days of data, the participants may be asked to repeat this measurement at an unscheduled visit.

Week 10/Week 18 (Visit 3): Gestational Age 34-36 weeks (Both Early GDM Dx and Regular GDM Dx)
RT-CGM and meter will be downloaded for the intervention group and meter downloaded for the control group. Vital signs, weight and medications and dose will be recorded at each visit and maternal ultrasound results if available (appendix M).
Questionnaire on nutrition and exercise in pregnancy and satifaction with CGM and lifestyle changes with CGM.
The control group will wear blinded CGM for 10 days and return during regularly scheduled OB visit. HgA1c and fructosamine will be collected.
The study staff will follow up with participants to remind them to return the devices. If for any reason, the CGM device fails to capture at least 3 days of data, the participants may be asked to repeat this measurement at an unscheduled visit.

Week 14 /Week 22 (Visit 4) Gestational Age 38- 40 weeks (Both Early GDM Dx and Regular GDM Dx)
RT-CGM and meter will be downloaded for the intervention group and meter downloaded for the control group. Vital signs, weight and and medications and dose will be recorded at each visit and results of maternal ultrasound if available (appendix M).

Between Visits: In the weeks between visits participants will continue their routine OB care with their OB providers. The OB providers may or may not be aware that their patient is participating in the study or have knowledge of their study group allocation. The participants will provide their OB providers the usual blood sugar values that they typically supply to their OB provider. For the control group this will be fingerstick glucose values for fasting and 1-hr post-meals. For the intervention group, this will be a log of the CGM

glucose values at the time of fasting and 1-hr post-meals. The OB providers will not be expected to use the CGM system itself.

Delivery: EMR will be reviewed for maternal and fetal outcomes.

I. Randomization/allotment: Randomization/allotment: Once they have signed the consent form, study participants will be randomized to treatment group. The project will use random, permuted blocks within strata to do this. Two participant factors will be considered in creating the strata: 1) weeks pregnant (14-24 weeks or 28 weeks); and 2) pre-pregnancy BMI (</= 35 and >35). Thus, the strata will be:

Pregnant 14-24 weeks and BMI ≤35
Pregnant >24 weeks and BMI ≤ 35
Pregnant 14-24 weeks and BMI >35
Pregnant >24 weeks and BMI >35.

Separate randomization lists will then be prepared for each of the above strata, using random permuted blocks generated in SAS 9.4. The lists will be transferred (by the statistician) to a sequence of sealed envelopes with the treatment group noted on a card within.

Since this is a small clinical trial, there is the potential problem of uneven distribution of study participants across the strata. However, we believe we have mitigated this potential by having only 4 strata. Also, this approach works better for this project than other approaches (such as the minimization method) due to the relatively greater level of staffing effort required for those approaches to work.

Source: Pocock SJ. 1983. Clinical Trials. A Practical Approach. Chistester, New York: John Wiley & Sons

J. Study Procedures, Materials and Devices :

Televisits:
Preference will be to conduct screening visits and all study visits in person coupled to standard OB visits. However as COVID-19 pandemic continues more OB patients are using telehealth visits for routine OB care. If patient is not scheduled for in person OB visit during study visit window then reseach visit will be scheduled via telehealth. The University of Washington uses the ZOOM platform which is HIPPA compliant and ensures patient privacy during the visit.

Medical Devices:

CGM (DEXCOM G6): A continuous glucose monitor (CGM) is a way to measure glucose levels in real-time throughout the day and night. A tiny electrode called a glucose sensor is inserted under the skin by a skin prick to measure glucose levels in tissue fluid. A small plastic piece of tubing remains inserted in the skin. Typically, one cannot feel this tubing once inserted. It is connected to a transmitter that sits on top of the skin and is about the size of a quarter. It is attached or secured by medical tape to the wearer's skin. It is approved for use on the abdomen for 10 days. The CGM either records the blood sugars which we will then download in our clinic at

study visit 2 (with de-identified data) or it sends the information via wireless radio frequency to a monitoring/display device or to a cellular phone so one can see their own data on their glucose and we can download it remotely. The device automatically generates an alert for glucose < 55, and an alert will also be generated for glucose > 140 in the unblinded portion of the study. The intervention group participants will be given a handout (Appendix K) for troubleshooting these alerts, particularly during the blinded portion of the study. DEXCOM G6 is FDA approved for use in patients with diabetes and will be used in accordance with instructions as approved for diabetes. It is not currently approved for patients with gestational diabetes but will be used in accordance with instructions as approved for diabetes. The risk is minimal with use of this device. In this study, we recommend patients connect the CGM to their cell phones, but if unable/unwilling, we will provide transmitters for participants to allow for real-time monitoring. Study staff will insert the first sensor for the groups and demonstrate how to insert additional sensors for the intervention group who will continue to use RT-CGM. If this is to be done as a televisit, the sensors, transmitter, and device (if needed) will be mail to the participant. Then the study staff will walk the participant through the first insertion through a virtual zoom visit. Patients will also have a youTube video available for reference for the patients. For the blinded control, the research coordinator will insert all sensors unless televisit is needed with procedure as above. The patients will be instructed on how to remove the sensor themselves after 10 days and bring back their scheduled OB visit. The intervention group will wear the RT-CGM continuously and change the sensor every 10 days for the duration of the pregnancy and have telephone support and may refer to the youTube video on insertion if needed. The intervention participants will have RT-CGM download serially over the study during regularly scheduled OB visits or televisits. The control group participants will wear the blinded CGM at beginning, at 30-32 and 34-36 weeks of the study. If, during the blinded portion of the study, due to device malfunction (rather than subject non-compliance), the device records less than 3 days of data, the participant can return to restart another 10 days of blinded CGM data.

The receiver and/or the app will display the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. The app provides the additional capability to share data with "followers" using the Dexcom Share service. The receiver can be put into a blinded mode using CLARITY® software. In this mode, users are unable to see the CGM data or receive CGM alerts.

CGM Ancillary Devices Dexcom CLARITY® is an accessory for users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow the use of the CGM data by the user and study clinicians. Target ranges of 65 to 140 mg/dl [3.6 to 7.8 mmol/l] will be set and the patients will be introduced to the use of alarm settings. Both participants and study sites will use CLARITY® to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode. A CLARITY® mobile app can be used for a retrospective review of glucose data on the smart device and can also be set up to allow receipt of push notifications of CGM data facilitating data review. For all patients (intervention and control group) an anonymized CLARITY® account will be created by using a sequential study number which is allocated at randomization.

Intervention Group:

- For participants who have a supported phone, the DEXCOM G6 CGM app will be installed on participant's smart phone.
- An anonymized CLARITY® mobile account will be set up and linked to the research site.
- Participants will use CGM data to log their blood sugars for fasting and 1-hour post-meals for review by their OB provider. The OB providers will not specifically use the CGM in their management decisions.
- A high alert threshold will be set at 140 mg/dl [7.8 mmol/l]. Low alert threshold and urgent low soon alerts will be turned off. If participants require insulin, the low alert will be turned on and the threshold set at 65 mg/dl [3.6 mmol/l]. In addition, the urgent low alert (55 mg/dl [3.1 mmol/l]), the urgent low soon alert (when glucose levels

are falling fast and will be below 55 mg/dl [3.1 mmol/l] in less than 20 min) as well as alerts for rise and fall rate (3 mg/dl [0.17 mmol/l]) in addition to alerts for signal loss and no readings for more than 20 min will be enabled.
- Participants with applicable smart phones may have CLARITY® push notifications on the CLARITY® mobile app about weekly time in range comparison enabled during the study.
- For app users, the "Share and Follow" functionality will be discussed and encouraged (i.e. the study participants are able to invite followers to review their glucose levels).
- For participants using the receiver only, the receiver will be downloaded into the CLARITY® clinic account at each visit. CGM data and reports. RT CGM-Participants will also keep a logbook of their blood sugars for their provider to review.

Control Group

The participants of the control group will perform self-monitored blood glucose testing with a study-provided blood glucose meter, including testing supplies. They will perform capillary blood glucose monitoring as routinely used for patients with GDM, i.e., at least four capillary blood glucose values daily including measurements in a fasting state as well as 1h after starting each meal. The study participants will keep a logbook of their glucose values

Each participant of the control group will be assigned a study blood glucose meter to measure and store their blood glucose values during the study.. A commercially available desktop software used in conjunction with the glucose meter for blood glucose monitoring will be utilized for downloading the meter data at each visit ensuring that dates and times are correct. Blood glucose meters used by the control group will be assessed to establish frequency of testing (overall and per week) as well as percentage of days with less than four measurements per day.

Subjects who got randomized to the control group then decided to withdraw from the study and discontinue their participating in the study will receive an email asking them to fill out a survey questionnaire to explain the main reason and any other reasons for withdrawal from the study. The survey will be sent to subjects' email through a link from Redcap and it won't take more than 10 minutes to complete.

Glucose Meter: A glucometer is a device for measuring the concentration of glucose in the blood by placing a small drop of blood on a disposable test strip where a chemical reaction with glucose alters the electrical conductivity of the strip. It records glucose and also records average glucose and standard deviation and goal range can be set and show time in range. This is standard of care for patients with gestational diabetes in pregnancy to check fasting and 1 or 2 hours post-meals.

Gestational DM Nutritional Classes:

As per local standard of care, nutritional counseling for GDM is provided to all patients with diagnosis of GDM and all participants will be offered and asked to complete this session. Completion of session will be assessed at visit 2.

RT-CGM Handout:

A simple educational handout has been developed to explain glucose goals in pregnancy and also how food and activity affects blood sugars. This handout will be reviewed with RT-CGM participants at visit 0 and adapted to fingersticks as well for the control group (see Appendix A1, A2)

K .Measurements (Appendix C): We will measure HbA1c and fructosamine at the beginning of the study period and HbA1C at 30-32 and HbA1C and fructoasmine at 34-36 weeks. At each visit, blood pressure, maternal resting heart rate, maternal weight and height will be measured. At baseline and 34-36 weeks,

questionnaires on diet and physical activity and personal wellness questionnaires will be obtained. In the intervention group at 34-36 weeks, a questionnaire about CGM technology and perception of benefit of CGM use will be obtained.

Anthropometrics: Height will be recorded in centimeters and inches by a stadiometer. **Weight** will be recorded in pounds and kilograms using a Digital scale. Two measurements will be taken, and the average will be used. **Blood pressure and pulse** are taken with an Professional Digital blood pressure machine. Two measurements will be obtained at each appointment. If performed via remote televisit then patients will use their own blood pressure cuff and available scale.

L.Collection of Human Biological Specimens:

Fingerstick and serum HbA1c and Fructoasmine: The HbA1c test is a blood test that provides information about a person's average levels of blood glucose over the last 3 months. Fructoasmine is a blood test that provides infromation about the average blood glucose over 2 weeks. The DCA Vantage Analyzer HbA1c assay tests for a quantitative determination of HbA1c in human whole blood, and provides immediate test results from a finger prick of blood. Serum HbA1c and fructoasmine is sent via LabCorp.

CBC: The complete blood count (CBC) is a test that evaluate the cells that circulate in blood, including red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs). CBC will be conducted at baseline and week 34-36.

M: Questionnaires

Nutrition Questionnaire (Appendix G):: Starting The Conversation (STC) is an eight-item simplified food frequency instrument designed and validated for use in primary care and health-promotion settings (12).

Physical Activity Questionnaire (Appendix H): The International Physical Activity Questionnaire (short) is a validated questionnaire that reviews the last 7 days of activity for middle aged adults (age 15-69 years) (13).

Diabetes Distress Questionnaire (Appendix O): Problem Areas in Diabetes Scale 5 (PAID-5), is a 5-item validated short form of the PAID-20. The PAID has been used in women with GDM. The questionnaire consists of 5 items, scored on a 5-point Likert scale ranging from 0 (not a problem) to 4 (a serious problem). Total scores can range from 0 to 20, with higher scores suggesting greater diabetes related distress. A cutoff of 8 or higher indicates elevated diabetes distress (14-15).

WHO-5 well-being index (appendix I) is a marker of overall welling and has been used to evaluate overall health in type 1 and type 2 diabetes (21)

Depressive Symptoms Questionnaire (Appendix P): The Patient Health Questionnaire 9 (PHQ-9) will be used. The PHQ-9 score ranges from 0 to 27: each of the 9 items is scored from 0 (not at all) to 3 (nearly every day), in which higher scores indicate more depressive symptoms Research has shown that a cutoff of 12 or higher is suitable to identify elevated depressive symptoms in patients with diabetes (15-18).

Perception/Satisfaction with CGM and Fingersticks/Meter (Appendices J): The Harvard Joslin Diabetes Center has developed a series of questionnaires on CGM experiences, opinions and expectations that will be given at the end of the intervention and has been adapted for the GDM. Additionally,questions about food changes and activity changes that was created for CGM use(19,20) . Questionanires have been adapted for use in those using only meter fingersticks and for GDM.

Sleep Questionnaire (**appendix Q**) The Pittsburgh Sleep Questionnaire is good tool for screening sleep disorders in the population and has been used in pregnancy (22,23)

N: Glucose/CGM Data /Evaluation Measures: The compliance and duration wear for participants with CGM will also be recorded. Glucose dynamics, e.g., average glucose, standard deviation, mean amplitude of glucose excursion (MAGE), time in range % (65 and 140 mg/dL), % high (>140 mg/dL)), % low (<64 mg/dL), and severe low % (<54mg/dL) and coefficient of variation (CV) and other statistical measures of glucose variability in those with CGM willbe reviewed from the RT- CGM device data at baseline and visit 2-4. Blinded CGM values will be obtained at baseline and visit 2 and 3.

Glucose meter: Compliance with fingersticks 4 times a day will be recorded by average number of fingersticks per day. Glucose data including: average glucose, standard deviation, mean amplitude of glucose excursion (MAGE), time in range % (65 and 140 mg/dL), % high (>140 mg/dL), % low (<64mg/dL), and severe low % (<54mg/dL) will also be recorded.

N:Antenatal Ultrasound Markers: estimated fetal weight (in grams and percentile) using Hadlock scale, Biparietal Diameter, Head circumference, abdominal circumference, and femur length. Amniotic Fluid Index.

O: Delivery Outcomes:

Obstetric Outcomes:
1.Gestational age at delivery
2.Labor status (spontaneous labor, induced labor, no labor). For induced labor include indication for induction
3,Mode of delivery (vaginal delivery, cesarean delivery, operative vaginal delivery) including indication for delivery
4.Shoulder dystocia: defined as a delivery that requires additional obstetric maneuvers to release the shoulders after gentle downward traction has failed. SD occurs when either the anterior or, less commonly, the posterior fetal shoulder impacts on the maternal symphysis or sacral promontory

Maternal Outcome:
1. Preeclampsia or GHTN
2. Maternal insulin or medication use
3. Maternal hypoglycemia: symptoms or asymptomatic biochemical hypoglycemia (fingerstick or RT-CGM less than 54 mg/dL (3.0 mmol/L), severe (fingerstick or RT-CGM < 64mg/dl (3.6 mmol/l)
4. Maternal weight gain

Fetal Outcome:
1. Gestational age at delivery
2. Live born or stillbirth

3. Birth weight: (large for gestational age, small for gestational age, macrosomia, birthweight ratio). Large for gestational age: birthweight > 90th centile for gestation using Fenton 2013 growth charts. Small for gestational age: birthweight below the 10th centile using Fenton 2013 growth charts. Macrosomia: birthweight ≥ 4 kg.
4. Birthweight ratio (birthweight adjusted for gestation and gender calculated with the Fenton 2013 web calculator (http://peditools.org/fenton2013).
5. 5- minute Apgar score
6. Respiratory distress
7. Neonatal hypoglycemia: defined as < 4 h of life: < 1.4 mmol/l (30 min after first feed); < 2.2 mmol/l (1 h after subsequent feeds), 4–24 h of life: < 1.9 mmol/l (prefeed); < 2.5 mmol/l (1 h after feed)
8. NICU admission including LOS
9. Birth injury (such as brachial plexus injury)
10. Hypoxic ischemic encephalopathy

P. Risks and Side Effects:

There are various possible risks and side effects that a participant may incur as a result of this study. At the beginning of the study, when participants are administered the informed consent form by research staff, they will be informed that their participation is completely voluntary and will be informed of the risks and benefits. They are free to leave the study at any time and will not be penalized. Potential subjects will also be told that failure to participate in no way affects the usual care they would receive from their OB provider. Only after all questions have been answered, both study staff and the participant will sign and date the consent form.

It is very unlikely that there will be any adverse events

There are possible risks associated with the intervention activities, including the medical device, including:

a. Less Likely (1% ≤ Event Rate < 5%): CGM site infection or tape allergy (<1-2%) (41)
b. Likely (5% ≤ Event Rate < 10%): None
c. More likely (Event Rate ≥ 10%): None

Risk to Participants:
There is the possibility of bruising, soreness and infection at the sites of needle sticks for blood draws, finger sticks for checking glucose levels and at the insertion sites of the CGM device. All participants will be provided with an emergency number for who to contact if any problems arise.

Continuous Glucose Monitoring Device: Participants may have temporary discomfort at the time of inserting the small filament. This can include bruising or redness of the skin, rare allergy to tape used to keep the device in place, infection at the insertion site, and potential perceived dislike of having a medical device on them for 10 days.

There is the risk of lightheadedness, dizziness and fainting from having blood drawn.

There is the possibility of potential embarrassment answering questionnaires. Participants are told they can leave questions blank if they are uncomfortable answering them.

There is the risk of anxiety because the medical history contains some sensitive questions like alcohol and drug history and questions about previous pregnancies.

There may be confusion about when to test blood sugar which could cause anxiety. Participants will be told to follow the instructions of their provider. Participants will be provided with study contacts for any questions and the study will work in conjunction with the participants' OB provider about blood sugar testing instructions.

There is the risk for participants in RT-CGM in the intervention group missing alerts if the alert notification is turned off.

There is the risk of lack of accuracy of the CGM read outs in the intervention group if the participant takes acetaminophen.

There is the risk for both groups if during insertion of the CGM the insertion wire breaks and becomes lodged under the skin and requires removal.

There are some skin issues that can occur when using the CGM device such as allergic reactions to the device that are localized and can include bruising, rash, soreness, and infection. This skin reaction can also be caused by the tape used to secure the device.

There is the risk of suicidal ideation presenting itself while answer the PHQ-9 questionnaire. If the subject endorses suicidal ideation answering the PHQ-9 our plan we be to call the participant immediately and discuss the participant's answer, provide the participant the number for a suicide hotline, and to call the PI if the participant endorses the intent to hurt themselves. The PI of the study will be notified immediately and will make the decision to call 911.
We will be checking for completion of the questionnaires after links to participants are sent to them and the PHQ-9 answers will be checked at that time. Our time frame for checking the PHQ-9's completion is within 3-5 days after being sent out. Our plan will be put into action if any questions are answered in a manner concerning to our study personnel who will be trained for our action plan and what to watch for within an hour of seeing the answer to the question

Body measurements: Participants may experience discomfort or embarrassment associated with weight and fundus measurements**.**

Q. Benefits:

Participants may receive some benefit for glucose control in pregnancy with RT-CGM which may or may not translate to improved fetal and maternal outcomes. Control patients will likely receive no benefit from blinded CGM and fingersticks 4 times a day fasting and post-meals as these are the current standard of care in GDM. This research may benefit society by enhancing our understanding of medical devices use in GDM and thus help establish new procedures and practices that are associated with GDM.

R. Conflicts Of Interest:

No conflicts of interest are noted.

S. Confidentiality:

All of the subjects' personal information, clinical data and consent documents will be stored in a secure location in a locked file cabinet in the University of Washington OB research coordinator's office. The subjects' personal information and research related clinical data other than routine laboratory results will be accessible only to the Principal Investigator and the research staff associated with the study. Organizations that may

inspect and copy the participant information include the IRB of the University of Washington. A master code linking the unique study numbers with subjects' identifying information will be kept by the Principal Investigator or by the Project Officer in a locked file cabinet. Additionally, all data collected by coordinators will be entered and managed through the encrypted Research Electronic Data Capture (REDCap) system maintained at University of Washington. All data is de-identified with no personal health information entered (PHI). REDCap was developed specifically around HIPAA security guidelines. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. REDCap servers are housed in a local data center at CNMC, and all web-based information transmission is encrypted. This system is accessed through a secure login and password. Only the RedCap database coordinators and study staff will have access privileges to the University of Washington data set and will be strictly prohibited from sharing passwords. All will undergo the standardized authorized training provided by the REDCap team. Staff will maintain files in password-protected documents on HIPAA-compliant servers. REDCap programmers build in quality controls for the data that will be collected according to their stringent protocols. Data will be stored for 3 years after study completion for possible re-analysis and sub-group analysis that the clinical team may determine to be useful. More information about the consortium and system security can be found athttp://www.projectredcap.org. Dr. Ehrhardt and her research team will destroy the informed consent, research source documents, data files, and master code 3 years after the completion of the study. This will allow time for the PI and collaborators to reexamine the data as needed in the revision process for manuscripts submitted to peer-reviewed journals.

All information that the study subjects provide study personnel is for research purposes only and, as such, names and any other identifying information will not be reported or published in papers, presentations, or proposals that result from this research.

When the subject enrolls in the study, she will be assigned a unique study number that is not any part of her social security number or other personal identifier. These unique study numbers will be used to identify all information that subjects provide and any information that is collected from their medical records. The unique study numbers will be assigned sequentially according to the order of study enrollment and subjects will be identified by the initials of the group to which they are randomized and 3 numbers according to their entry into the study beginning with 001. Therefore, the first subject randomized to the DMC (control) group willl be DMC-001 and the first subject randomized to the DMCGM (intervention) group will be DMCGM-001. A total of 50 DMC and 50 DMCGM subjects will be enrolled.

Although every precaution is being taken to protect participant privacy, breach of confidentiality is always possible. In the unlikely event of a breach of confidentiality, the nature of the research data is not of a sufficiently personal nature to negatively affect employment status, lead to civil/criminal liability, incur financial risks to the study participants, or other risks.

T. Subject Compensation:

Participants will be given $50 after visit 0 and $50 after visit 3. Visit 3 compensation will be given to participant upon return of blinded device or RT-CGM download at 34-36 weeks. If lack of CGM data necessitates unscheduled visits, the participant will receive an additional $25 per visit up to a maximum of $50 if 2 unscheduled visits are required. Subjects will also have use of the medical devices during the study for free: in the intervention group they will receive a glucose meter and test strips (total 50 test strips for free) to be used as needed. In the control group they will receive a glucose meter and 400 test strips for free if not covered by their insurance. No additional cost will be incurred by subjects.

If extra visits are necessary we will follow the OB clinic guidelines for COVID 19 screening. This money can be used for travel and parking but all study visits are piggy backed to a regular clinic visit so no extra travel or parking is required by the study although visits may be a little longer than usual

U. Appendix:

A. Educational Material: Real-Time Continuous Glucose Monitoring educational material (A1) or Fingerstick educational material (A2)

B. Table of Study Measurements

C. Pre-Screening Checklist Telephone

D. Medical History and Screening Form

E. Medical History and follow up form /insulin use

F. Nutrition/Food Questionnaire

G. Physical Activity Questionnaire

H. Glucose Log Form

I. WHO QOL 5- question form

J. CGM and Fingerstick Perception Questionnaire

K. CGM Device Troubleshooting Handout

L. Adverse Events Log

M. Diabetes Distress Questionnaire

N. PHQ-9 Depression Questionnaires

O. Sleep questionnaire

P. Consent

Q. References

R. Flier patient

S. Labor & Delivery Clinical Research, COVID-19 –Phase 1 Return to Work Guidance

T. Data and Safety Monitoring Plan

U. Participant Contact Information Sheet

V. Dex-Com G6 Users Guide

W. Suicide Plan